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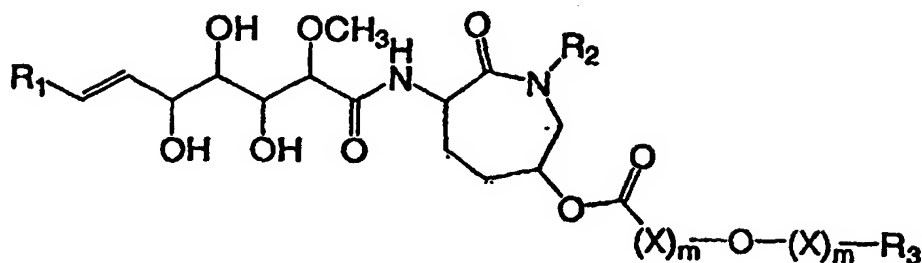
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(54) Title: SUBSTITUTED CAPROLACTAM CARBONATES AND ETHERS AND THEIR USE AS ANTI-TUMOR AGENTS



(I)

(57) Abstract: The present invention relates to certain substituted caprolactam carbonate and ether compounds of following formula (I): pharmaceutical compositions containing said compounds, the use of said compounds in treating tumors and to a process for making said compounds.



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SUBSTITUTED CAPROLACTAM CARBONATES AND ETHERS AND THEIR USE AS ANTI-TUMOR AGENTS

FIELD OF THE INVENTION

The present invention relates to the area of chemotherapeutic agents and, more particularly, relates to certain substituted caprolactam carbonates and ethers, and the use of said caprolactam carbonates and ethers in treating tumors.

BACKGROUND OF THE INVENTION

Cancer is a serious health problem throughout the world. Cancer incidence in the U.S. has increased 30% during the past 30 years, and is expected to continue to increase into the next century. This is attributable to increased prevalence of cigarette smoking by women, general aging of the population, enhanced diagnostic capabilities and, as well, potential decreases in mortality from other causes. As a result, an extensive number of research endeavors have been undertaken in an effort to develop therapies appropriate to the treatment and prevention of cancer in humans.

In the chemotherapeutic area, research has been conducted to develop anti-tumor agents effective against various types of cancer. Oftentimes, anti-tumor agents which have been developed and found effective against cancer cells are, unfortunately, also toxic to normal cells. This toxicity manifests itself in weight loss, nausea, vomiting, hair loss, fatigue, itching, hallucinations, loss of appetite, etc., upon administration of the anti-tumor agent to a patient in need of cancer chemotherapy.

Furthermore, conventionally used chemotherapeutic agents do not have the effectiveness desired or are not as broadly effective against different types of cancers as desired. As a result, a great need exists for chemotherapeutic agents which are not only more effective against all types of cancer, but which have a higher degree of selectivity for killing cancer cells with no or minimal

effect on normal cells. In addition, highly effective and selective anti-tumor agents, in particular, against cancers of the colon, bladder, prostate, stomach, pancreas, breast, lung, liver, brain, testis, ovary, cervix, skin, vulva and small intestine are desired. Moreover, anti-tumor activity against colon, breast, lung and prostate cancers as well as melanomas are particularly desired because of the lack of any particular effective chemotherapy at the present time.

DESCRIPTION OF THE PRIOR ART

U.S. Patent No. 4,831,135 discloses novel δ -caprolactam derivatives with anti-tumor, antibiotic and anthelmintic activity.

J. Org. Chem., Vol. 51, pages 4494-4496 (1986) discloses the isolation and identification of certain caprolactam natural products which exhibit antiproliferative activity against eucaryotic cells, nematodes, and bacteria.

J. Am. Chem. Soc., Vol. 111, pages 647-654 (1989) discloses the isolation and identification of certain caprolactam natural products.

J. Org. Chem., Vol. 55, pages 240-242 (1990) discloses the isolation and identification of certain caprolactam natural products which exhibit antiproliferative activity against nematodes and bacteria.

J. Nat. Prod., Vol. 60, pages 814-816 (1997) discloses the isolation and identification of certain caprolactam marine natural products.

J. Chem. Soc., Perkin Trans. 1 Issue 22, pages 2849-2854 (1995) discloses a process for preparing the caprolactam compound (+)-bengamide E.

J. Org. Chem., Vol. 60, pages 5910-5918 (1995) discloses a process for preparing the caprolactam compound (+)-bengamide E.

Heterocycles, Vol. 38, pages 2383-2388 (1994) discloses a process for preparing the caprolactam compound bengamide B.

Tetrahedron Lett., Vol. 35, pages 6899-6902 (1994) discloses a process for preparing the caprolactam compound bengamide E.

Syn. Lett., Issue 12, pages 1007-1008 (1992) discloses a process for preparing the caprolactam compound bengamide E.

J. Chem. Soc., Chem. Commun., Issue 15, pages 1064-1066 (1992) discloses a process for preparing the caprolactam compound bengamide A.

J. Org. Chem., Vol. 57, pages 5042-5044 (1992) discloses a process for preparing the caprolactam compound bengamide E.

Tetrahedron Lett., Vol. 32, pages 5907-5910 (1991) discloses a process for preparing the caprolactam compounds bengamide E and B.

Tetrahedron Lett., Vol. 32, pages 3409-3412 (1991) discloses a process for preparing an intermediate useful for preparing the bengamide class of caprolactam compounds.

Tetrahedron Lett., Vol. 32, pages 1063-1066 (1991) discloses a process for preparing the caprolactam compound bengamide E.

J. Nat. Prod., Vol. 62, pages 1691-680 (1999) discloses the isolation and identification of certain caprolactam marine natural products.

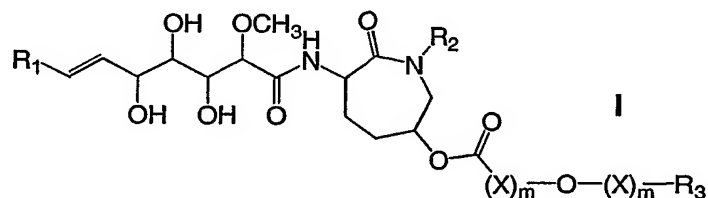
J. Nat. Prod., Vol. 62, pages 678-1693 (1999) discloses the isolation and identification of certain caprolactam marine natural products.

SUMMARY OF THE INVENTION

The present invention provides new anti-tumor agents which are effective against a variety of cancer cells. More particularly, the present invention relates to certain substituted caprolactam carbonates and ethers which exhibit a higher degree of selectivity in killing cancer cells. In addition, the present invention provides pharmaceutical compositions useful in treating tumors comprising a therapeutically effective amount of a certain substituted caprolactam carbonates and ethers. Moreover, the present invention provides a method of treating tumors comprising administering to a mammal afflicted therewith a therapeutically effective amount of certain substituted caprolactam carbonates and ethers. Furthermore, the present invention relates to a process for preparing certain substituted caprolactam carbonates and ethers.

DETAILED DESCRIPTION OF THE INVENTION

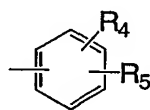
The essence of the instant invention is the discovery that certain substituted caprolactam carbonates and ethers are useful in treating tumors. In one embodiment, the instant invention provides new anti-tumor agents of formula I:



where

- R_1 is (C_{1-6}) alkyl or (C_{3-6}) cycloalkyl;
- R_2 is hydrogen or (C_{1-6}) alkyl;
- each X, independently, is (C_{1-12}) alkylene;
- each m, independently, is 0 or 1;

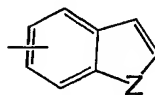
and R_3 is (C_{1-12}) alkyl; (C_{2-12}) alkenyl; (C_{2-12}) alkynyl; (C_{3-8}) cycloalkyl; or an aromatic ring system selected from II, III, IV and V:



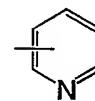
II



III



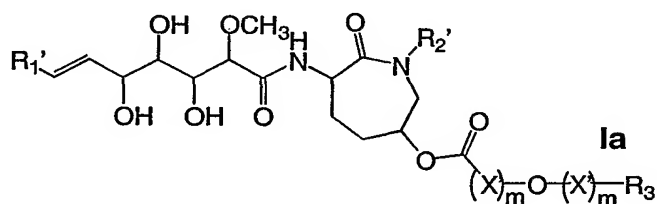
IV



V

where R_4 is hydrogen, chloro, or methoxy; R_5 is hydrogen, chloro, (C_{1-18}) alkyl or (C_{1-18}) alkoxy; and Z is oxygen, sulfur, N-H, or N-CH₃; or a pharmaceutically acceptable acid addition salt thereof, where possible.

Preferred compounds are those of formula Ia:



where each m, independently, and R_3 are as defined above;

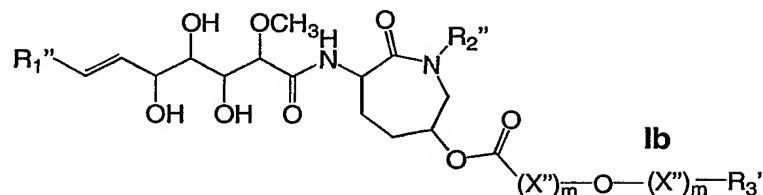
R_1' is (C_{1-6}) alkyl;

R_2' is hydrogen or (C_{1-4}) alkyl;

and each X' , independently, is (C_{1-6}) alkylene;

or a pharmaceutically acceptable acid addition salt thereof, where possible.

More preferred compounds are those of formula Ib:



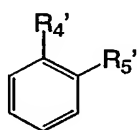
where

each m, independently, is as defined above;

R₁'' is *i*-propyl or *t*-butyl;

R₂'' is hydrogen or methyl;

R₃' is (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₅₋₇)cycloalkyl; or an aromatic ring system selected from IIa and V:



IIa



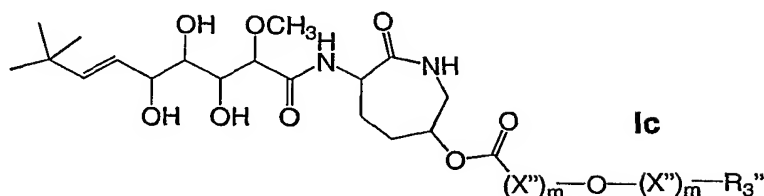
V

where R₄' is in the *meta* position and is hydrogen or chloro; and R₅' is in the *para* position and is hydrogen, chloro, (C₁₋₁₈)alkyl or (C₁₋₁₈)alkoxy;

and each X'', independently, is (C₁₋₆) alkylene;

or a pharmaceutically acceptable acid addition salt thereof, where possible.

Even more preferred compounds are those of formula Ic:



where each m , independently, is as defined above;

R_3' is (C_{1-6}) alkyl, (C_{5-7}) cycloalkyl, phenyl, 3,4-dichlorophenyl, 4-methoxyphenyl, 4-*n*-decylphenyl, 4-*n*-decyloxyphenyl or 3-pyridyl;

and each X'' , independently, is as defined above.

In another embodiment, the instant invention provides pharmaceutical compositions useful in treating tumors comprising a pharmaceutically acceptable carrier or diluent and a therapeutically effective amount of a compound of formula I above, or a pharmaceutically acceptable acid addition salt thereof, where possible, preferably a compound of formula Ia above, or a pharmaceutically acceptable acid addition salt thereof, where possible, more preferably a compound of formula Ib above, or a pharmaceutically acceptable salt thereof, where possible, and even more preferably a compound of formula Ic above, or a pharmaceutically acceptable acid addition salt thereof, where possible.

In still another embodiment, the instant invention provides a method for treating tumors comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of formula I above, or a pharmaceutically acceptable acid addition salt thereof, where possible, preferably a compound of formula Ia above, or a pharmaceutically acceptable acid addition salt thereof, where possible, more preferably a compound of formula Ib above, or a pharmaceutically acceptable acid addition salt thereof, where possible, and even more preferably a compound of formula Ic above, or a pharmaceutically acceptable acid addition salt thereof, where possible.

In the above definitions: 1) the alkyl groups containing 1 to 6 carbon atoms are either straight or branched chain, of which examples of the latter include isopropyl, isobutyl, *t*-butyl, isopentyl, neopentyl, isohexyl, 3-methylpentyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl and 1,1,2,2-tetramethylethyl; and 2) the alkyl and alkoxy groups containing 1 to 18 carbon atoms are either straight or branched chain.

The term “(C₁₋₁₂) alkylene” as used herein refers to a straight or branched chain divalent group consisting solely of carbon and hydrogen and having from 1 to 12 carbon atoms. Examples of “alkylene” groups include methylene, ethylene, propylene, butylene, pentylene, 3-methylpentylene, etc.

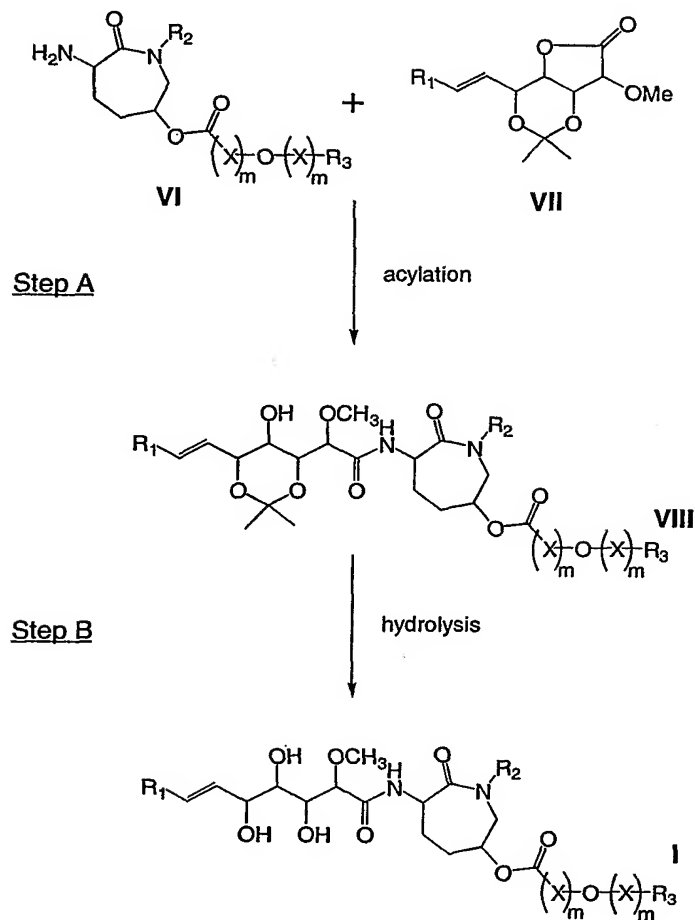
The term “(C₁₋₁₂) alkyl” as used herein refers to a straight or branched chain group consisting solely of carbon and hydrogen and having from 1 to 12 carbon atoms. Examples of “alkyl” groups include methyl, ethyl, propyl, butyl, pentyl, 3-methylpentyl, etc.

The term “(C₂₋₁₂) alkenyl” as used herein refers to a straight or branched chain group consisting solely of carbon and hydrogen, containing at least one carbon-carbon double bond, and having from 2 to 12 carbon atoms. Examples of “alkenyl” groups include ethenyl, propenyl, butenyl, pentenyl, 3-methylpentenyl, etc.

The term “(C₂₋₁₂) alkynyl” as used herein refers to a straight or branched chain group consisting solely of carbon and hydrogen, containing at least one carbon-carbon triple bond, and having from 2 to 12 carbon atoms. Examples of “alkynyl” groups include ethynyl, propynyl, butynyl, pentynyl, 3-methylpentynyl, etc.

The acid addition salts of the compounds of formula I may be those of pharmaceutically acceptable organic or inorganic acids. Although the preferred acid addition salts are those of hydrochloric and methanesulfonic acid, salts of sulfuric, phosphoric, citric, fumaric, maleic, benzoic, benzenesulfonic, succinic, tartaric, lactic and acetic acid may also be utilized.

The caprolactam carbonates and ethers of formula I may be prepared as depicted below:



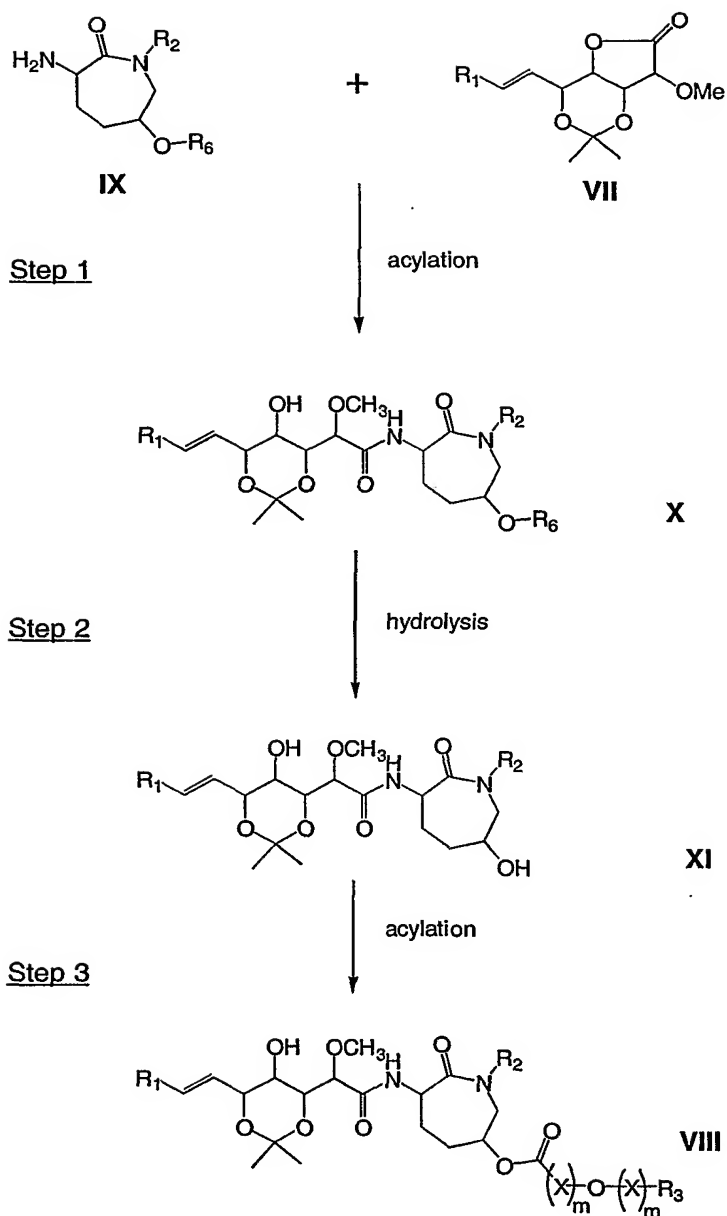
where each R_1 , R_2 , X , m and R_3 is as defined above.

As to the individual steps, Step A involves the acylation of an aminocaprolactam of formula VI with a lactone compound of formula VII to obtain a diamide compound of formula VIII. The acylation is conducted in the presence of: 1) a weak base, preferably a carboxylate salt such as sodium 2-ethylhexanoate; 2) a coupling agent, preferably a hydroxy compound such as 2-hydroxypyridine; and 3) a polar, organic solvent, preferably an ester such as ethyl acetate, at a temperature of between 0 °C and 50 °C, preferably at 25 °C, for a period of between 1 hour and 7 days, preferably for 72 hours.

Step B concerns the hydrolysis of the 1,3-dioxane group common to a diamide compound of formula VIII, to obtain a substituted caprolactam compound of formula I. The hydrolysis is typically carried out by dissolving the diamide in a mixture of solvents consisting of 1) a protic acid, preferably an organic acid such as trifluoroacetic acid, 2) a protic solvent, preferably water, and 3) an inert organic solvent, preferably a cyclic ether such as tetrahydrofuran, at a temperature of between 0 °C and 25 °C for a period of between 5 minutes and 2 hours.

Alternatively, the diamide compounds of formula VIII may be prepared according to the following 3-step reaction scheme:

11



where R_3 and each X , m , R_1 and R_2 are as defined above, and R_6 is an alcohol protective group. Preferably, R_6 is a silyl group such as *tert*-butyldimethylsilyl.

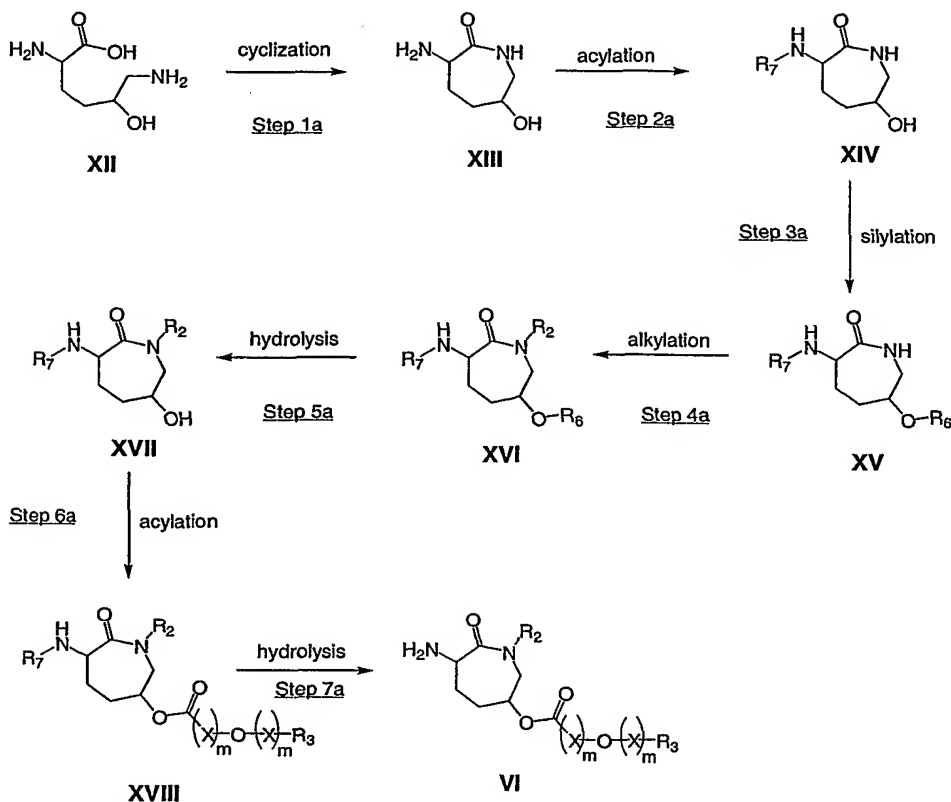
As to the individual steps, Step 1 involves the acylation of an aminocaprolactam of formula IX with a lactone compound of formula VII to obtain a diamide compound of formula X. The acylation is

conducted in the presence of a base, preferably an alkylamine base such as diisopropylethylamine, and a polar, organic solvent, preferably a protic polar solvent such as isopropanol, at a temperature slightly below or at the reflux temperature of the solvent employed for a period of between 4 and 48 hours.

Step 2 concerns the hydrolysis of the group R_6 common to a diamide compound of formula X to obtain a hydroxycaprolactam compound of formula XI. The hydrolysis is typically carried out in the presence of fluoride, preferably a fluoride salt such as tetrabutylammonium fluoride, and an inert organic solvent, preferably a cyclic ether such as tetrahydrofuran, at a temperature of between 0 °C and 25 °C for a period of between 5 minutes and 2 hours.

Step 3 concerns the acylation of a hydroxycaprolactam compound of formula XI by reacting it with a carbonyl chloride of formula $R_3(X)_mO(X)_mC(O)Cl$ where R_3 , and each X and m are as defined above, to obtain a diamide compound of formula VIII. The acylation is conducted in the presence of a base, preferably an alkylamine base such as triethylamine, and an inert organic solvent, preferably a chlorinated alkane such as dichloromethane, at a temperature of between -78 °C and 25 °C for a period of between 1 and 24 hours.

The aminocaprolactam compounds of formula VI may be prepared as depicted below:



where each R_6 , R_2 , X , m and R_3 is as defined above, and each R_7 is a carbonyl-containing group. Preferably, R_7 is an alkoxy carbonyl such as *t*-butoxycarbonyl.

As to the individual steps, Step 1a involves the cyclization of hydroxylysine (or any salt or hydrate preparation thereof) XII to obtain hydroxycyclohexyllysine XIII. The cyclization is typically carried out in the presence of a coupling reagent, preferably a diimide such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, and a suitable activating agent common to diimide coupling reactions, preferably an *N*-hydroxy compound such as 1-hydroxybenzotriazole hydrate, and a base, preferably an alkylamine base such as triethylamine, and a polar organic solvent, preferably an amide such as *N,N*-dimethylformamide, at a temperature of between 0 °C and 40 °C for a period of between 12 and 72 hours.

Step 2a involves the *N*-acylation of hydroxycyclolysine XIII to obtain an *N*-acylhydroxycyclolysine compound of formula XIV. The acylating agent is typically a carbonyl chloride. When R_7 is *t*-butyloxycarbonyl, the acylating agent is di-*tert*-butyldicarbonate. The reaction is carried out in the presence of a base, preferably an alkylamine base such as triethylamine, and a polar organic solvent, preferably an amide such as *N,N*-dimethylformamide, at a temperature of between 0 °C and 40 °C for a period of between 1 and 24 hours.

Step 3a involves the *O*-silylation of an *N*-acylhydroxycyclolysine compound of formula XIV to obtain a silyl ether compound of formula XV. The silylating agent is typically a silyl chloride or trifluoromethanesulfonate. When R_6 is *tert*-butyldimethylsilyl, the silylating agent is *tert*-butyldimethylsilylchloride. The reaction is carried out in the presence of a base, preferably a mild base such as imidazole, and a polar organic solvent, preferably an amide such as *N,N*-dimethylformamide, at a temperature of between 0 °C and 40 °C for a period of between 1 and 24 hours.

Step 4a involves the *N*-alkylation of a silyl ether compound of formula XV with an alkyl (defined as R_2 above) halide or sulfonate to obtain an *N*-alkyl caprolactam compound of formula XVI. The alkylation is conducted in the presence of a strong base, preferably an alkali metal amide such as sodium bis(trimethylsilyl)amide, and an inert organic solvent, preferably a cyclic ether such as tetrahydrofuran, at a temperature of between -100 °C and 25 °C for a period of between 5 minutes and 2 hours.

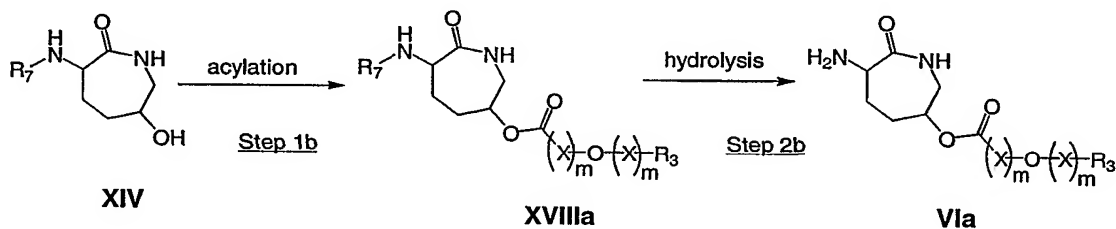
Step 5a concerns the hydrolysis of the group R_6 common to an *N*-alkyl caprolactam compound of formula XVI, to obtain a hydroxycaprolactam compound of formula XVII. The hydrolysis is typically carried out in the presence of fluoride, preferably a fluoride salt such as tetra-*n*-butylammonium fluoride, and an inert organic solvent, preferably a cyclic ether such as tetrahydrofuran, at a temperature of between 0 °C and 25 °C for a period of between 5 minutes and 2 hours.

Step 6a concerns the acylation of a hydroxycaprolactam compound of formula XVII to obtain an ester compound of formula XVIII by reacting it with carbonyl chloride of formula $R_3(X)_mO(X)_mC(O)Cl$ where R_3 , and each *X* and *m* are as defined above, in the presence of a

base, preferably an alkylamine base such as triethylamine, and an inert organic solvent, preferably a chlorinated alkane such as dichloromethane, at a temperature of between -78°C and 25°C for a period of between 1 and 24 hours.

Step 7a concerns the hydrolysis of the group R_7 on an ester compound of formula XVIII to obtain an aminocaprolactam compound of formula VI. The hydrolysis is typically carried out in the presence of a protic acid, preferably an organic acid such as trifluoroacetic acid, hydrogen or a silyl halide, preferably a silyl iodide such as trimethylsilyl iodide, and an inert organic solvent, preferably a chlorinated alkane such as dichloromethane, at a temperature of between -100°C and 25°C for a period of between 1 minute and 2 hours.

The aminocaprolactam compounds of formula VIa may be prepared as depicted below:



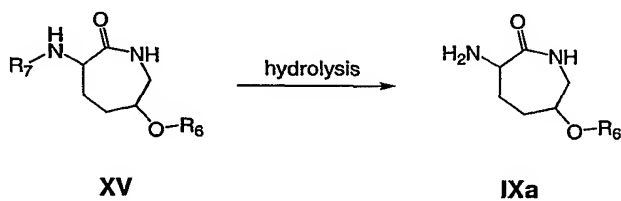
where each R_7 , X, m, and R_3 is as defined above.

As to the individual steps, Step 1b concerns the acylation of a hydroxycaprolactam compound of formula XIV to obtain an ester compound of formula XVIIIa by reacting it with a carbonyl chloride of formula $\text{R}_3(\text{X})_m\text{O}(\text{X})_m\text{C}(\text{O})\text{Cl}$ where R_3 , and each X and m are as defined above, in the presence of a base, preferably an alkylamine base such as triethylamine, and an inert organic solvent, preferably a chlorinated alkane such as dichloromethane, at a temperature of between -78°C and 25°C for a period of between 1 and 24 hours.

Step 2b concerns the hydrolysis of the group R_7 on an ester compound of formula XVIIIa to obtain an aminocaprolactam compound of formula VIa. The hydrolysis is typically carried out in the presence of an protic acid, preferably an organic acid such as trifluoroacetic acid, hydrogen or a silyl halide, preferably a silyl iodide such as trimethylsilyl iodide, and an inert organic solvent,

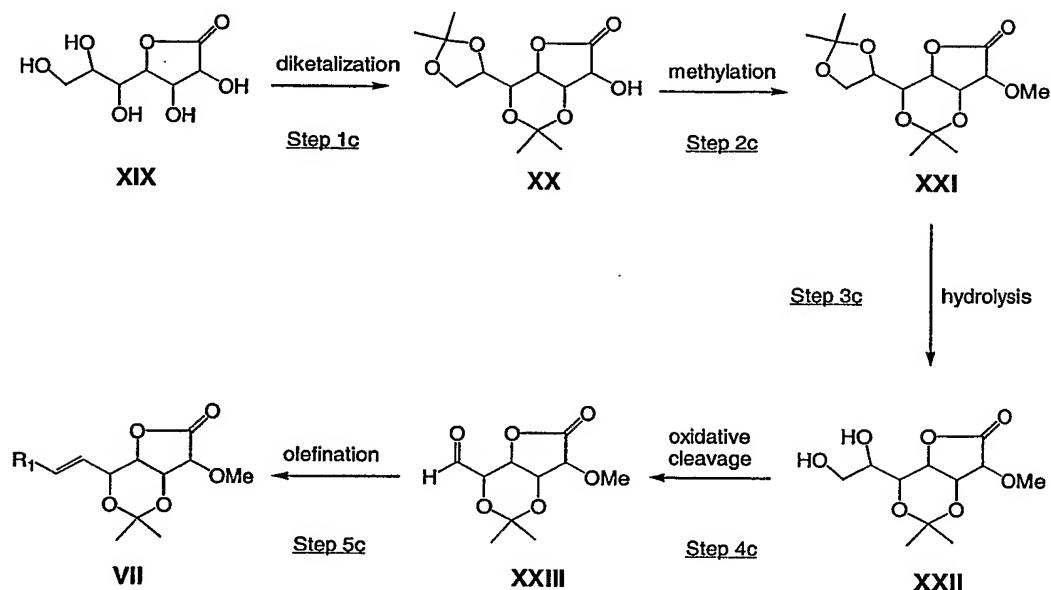
preferably a chlorinated alkane such as dichloromethane, at a temperature of between -100 °C and 25 °C for a period of between 1 minute and 12 hours.

The aminocaprolactam compounds of formula IXa may be prepared as depicted below:



where R_7 and each R_6 are as defined above. The reaction concerns the hydrolysis of the group R_7 on an ester compound of formula XV to obtain an aminocaprolactam compound of formula IXa. The hydrolysis is typically carried out in the presence of a protic acid, preferably an organic acid such as trifluoroacetic acid, hydrogen or a silyl halide, preferably a silyl iodide such as trimethylsilyl iodide, and an inert organic solvent, preferably a chlorinated alkane such as dichloromethane, at a temperature of between -100 °C and 25 °C for a period of between 1 minute and 2 hours.

The lactone compounds of formula VII may be prepared as depicted below:



where R₁ is as defined above.

As to the individual steps, Step 1c involves the diketalization of polyhydroxylated lactone of formula XIX with acetone to obtain *bis*(acetonide) XX. The diketalization is conducted in acetone as solvent using a catalyst such as iodine at a temperature of between 0 °C and the reflux temperature for a period of between 2 and 48 hours.

Step 2c involves the methylation of *bis*(acetonide) XX with a methylating agent such as methyl iodide to obtain the methyl ether XXI. The methylation is conducted in the presence of water and a base, preferably a metal oxide such as silver oxide, and an inert organic solvent, preferably a chlorinated alkane such as dichloromethane, at a temperature of between 0 °C and the reflux temperature for a period of between 12 hours and 7 days.

Step 3c involves the hydrolysis of methyl ether XXI to obtain the dihydroxy compound of formula XXII. The hydrolysis is conducted in the presence of water and a protic acid, preferably a

carboxylic acid such as acetic acid, at a temperature of between 5 °C and 35 °C for a period of between 1 and 24 hours.

Step 4c involves the oxidative cleavage of dihydroxy compound XXII to obtain the aldehyde XXIII. The reaction is conducted in the presence of an oxidant, preferably a periodate salt such as sodium periodate, in a protic solvent, preferably an alkanol such as methanol, at a temperature of between 0 °C and 25 °C for a period of between 10 minutes and 4 hours.

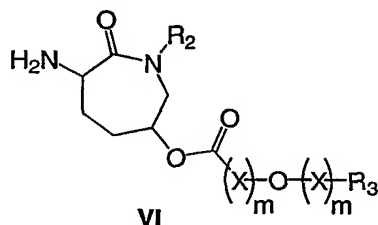
Step 5c involves the olefination of aldehyde XXIII to obtain a lactone compound of formula VII. The olefination is conducted in the presence of an organometallic compound, preferably an organochromium compound such as the transient species generated from chromium(II)chloride and a diiodoalkane (defined as R_1CHI_2 where R_1 is as defined above), in the presence of a solvent mixture consisting of 1) a polar organic solvent, preferably an amide such as *N,N*-dimethylformamide, and 2) an inert organic solvent, preferably a cyclic ether such as tetrahydrofuran, at a temperature of between -80 °C and 25 °C for a period of between 5 minutes and 4 hours.

Although the product of each reaction described above may, if desired, be purified by conventional techniques such as chromatography or recrystallization (if a solid), the crude product of one reaction is advantageously employed in the following reaction without purification.

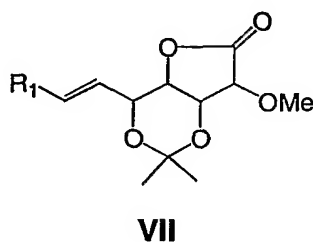
As is evident to those skilled in the art, the substituted caprolactam compounds of formula I contain asymmetric carbon atoms. It should be understood, therefore, that the individual stereoisomers are contemplated as being included within the scope of this invention.

As indicated above, certain of the compounds of formula I form pharmaceutically acceptable acid addition salts. For example, the free base of a compound of formula I can be reacted with hydrochloric acid to form the corresponding hydrochloride salt form, whereas reacting the free base of the compound of formula I with methanesulfonic acid forms the corresponding mesylate salt form. All pharmaceutically acceptable addition salt forms of the compounds of formula I are intended to be embraced by the scope of this invention.

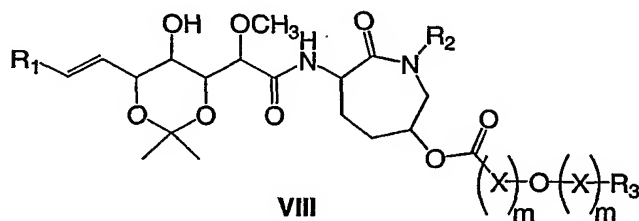
In a further embodiment, the present invention relates to a process for preparing a caprolactam compound of formula I which comprises, in a first step, acylating an amino caprolactam compound of formula VI



with a lactone compound of formula VII



in the presence of a polar, organic solvent to obtain a diamide compound of formula VIII



where each of R_1 , R_2 , X , m and R_3 are as defined above and, in a second step, hydrolyzing the diamide compound obtained in the first step by dissolving it in a mixture of solvents to obtain the desired caprolactam compound of formula I. Preferably, the acylation in the first step is conducted in the presence of: 1) a weak base, preferably a carboxylate salt such as sodium 2-ethylhexanoate; 2) a coupling agent, preferably a hydroxy compound such as 2-hydroxypyridine; and 3) a polar, organic solvent, preferably an ester such as ethyl acetate, at a temperature of

between 0 °C and 50 °C, preferably at 25 °C, for a period of between 1 hour and 7 days, preferably for 72 hours, whereas the hydrolysis in the second step is conducted in a mixture consisting of a protic, organic acid, a protic solvent and an inert, organic solvent, more preferably a mixture consisting of trifluoroacetic acid, water and tetrahydrofuran.

As indicated above, all of the compounds of formula I, and their corresponding pharmaceutically acceptable acid addition salts, are anti-tumor agents and are, therefore, useful in inhibiting the growth of various lymphomas, sarcomas, carcinomas, myelomas, and leukemia cell lines. The anti-tumor activity of the compounds of formula I may be demonstrated employing the Anchorage Dependent Growth Monolayer Assay (ADGMA) which measures the growth inhibitory effects of test compounds on proliferation of adherent cell monolayers. This assay was adapted from the 60 cell line assay used by the National Cancer Institute (NCI) with the following modifications: 1) cell lines representative for the important tumor types, viz., MDA-MB-435 human breast, A549 non-small cell lung, H1299 lung, HCT-116 colon and PC-3 prostate carcinomas, and U2OS osteosarcomas were utilized; and 2) a tetrazolium derivative, viz., 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium, inner salt (MTS), was utilized to determine cell density.

The ADGMA compares the number of viable cells following a 3-day exposure to a test compound relative to a number of cells present at the time the test compound was added. Cell viability is measured using a tetrazolium derivative, viz., MTS, that is metabolically reduced in the presence of an electron coupling agent (PMS; phenazine methosulfate) by viable cells to a water-soluble formazan derivative. The absorbance at 490 nm (A_{490}) of the formazan derivative is proportional to the number of viable cells. The IC_{50} for a test compound is the concentration of compound required to reduce the final cell number to 50% of the final control cell number. If cell proliferation is inhibited, the assay further defines compounds as cytostatic (cell number after 3-day compound incubation > cell number at time of compound addition) or cytotoxic (cell number after 3-day compound incubation < cell number at time of compound addition).

The MDA-MB-435 human breast carcinoma and the A549 non-small cell lung carcinoma lines were obtained from the American Type Culture Collection (ATCC) and used between passages 4-20 following thawing. MDA-MB-435 human breast carcinoma and A549 non-small cell lung

carcinoma cells were maintained and plated in DME/F12 medium containing 10% fetal bovine serum, 15 mM HEPES (pH=7.4), 100 units/mL penicillin, and 100 µg/mL streptomycin.

The H1299 lung, HCT-116 colon, and PC-3 prostate carcinoma cell lines, and U2OS osteosarcoma cell line were obtained from the American Type Culture Collection (ATCC) and used between passages 4-20 following thawing. H1299 and HCT-116 cells were maintained in RPMI 1640 containing 10% FBS, 100 units/mL penicillin and 100 µg/mL streptomycin; PC-3 cells were maintained in Kahn's Modification containing 10% FBS, 100 units/mL penicillin and 100 µg/mL streptomycin; and U2OS cells were maintained in DMEM containing 10% FBS, 100 units/mL penicillin and 100 µg/mL streptomycin.

Cell lines are trypsinized and counted using a Coulter counter to determine plating densities. Cells are then plated in their respective maintenance media (100 µL/well) in 96 well plates at the following densities: MDA-MB-435 and U2OS, 3,000 cells/well; A549 and HCT-116, 700 cells/well; H1299, 1,000 cells/well; and PC-3, 2500 cells/well. The number of cells plates as determined in preliminary experiments, results in cell densities of 75-90% of confluency by 4 days after plating. Initial cell densities, assayed one day after plating, are roughly 0.15-0.20 absorbance units greater than the media blank. Ninety-six well plates are seeded on day 0 and the test compounds are added on day 1. A control plate is created for each cell line that receives media only in row A and cells in row B. One day following plating, test compounds are added (in a final volume of 100 µL) to the test plates. Control plates receive 10 µL MTS mixture (prepared fresh on day of addition to cell plates at a ratio of 10 µL of a 0.92 mg/mL solution of PMS to a 190 µL of a 2 mg/mL solution of MTS) and 100 µL media. A_{490} of control plates is read 4 h after MTS addition to determine initial cell density values for each cell line. Three days after addition of test compound, 10 µL/well of MTS mixture is added to the test plates and A_{490} is read 4 h later. A_{490} values for wells containing cells are corrected for media absorbance, then normalized to initial density readings to determine percent net growth. IC_{50} values are determined from graphs of percent net growth as a function of compound concentration. Percent net growth is calculated as $(\text{Cell} + \text{Drug } A_{490} - \text{Initial } A_{490}) / (\text{Cell} + \text{Drug Vehicle } A_{490} - \text{Initial } A_{490}) \times 100\%$.

The following IC₅₀ values (average \pm S.D.) in μ M were obtained:

Compound	MDA-MB-435	A549	H1299	HCT-116	PC-3	U2OS
Ex. 1	0.21 \pm 0.14	N.T.	0.57 \pm 0.22	0.53 \pm 0.35	N.T.	>1
Ex. 2	0.07 \pm 0.02	0.117 \pm 0.02	0.21 \pm 0.17	0.17 \pm 0.1	N.T.	0.09 \pm 0.03
Ex. 3	0.08 \pm 0.03	0.132 \pm 0.02	0.33 \pm 0.27	0.16 \pm 0.03	N.T.	0.31 \pm 0.04
Ex. 4	0.13 \pm 0.07	0.158 \pm 0.016	0.17 \pm 0.13	0.08 \pm 0.01	0.08	0.25 \pm 0.14
Ex. 5	0.12 \pm 0.02	0.138 \pm 0.008	0.36 \pm 0.12	0.27 \pm 0.1	N.T.	0.62 \pm 0.16
Ex. 6	0.35 \pm 0.11	0.441 \pm 0.063	0.57 \pm 0.29	0.4 \pm 0.12	N.T.	0.77 \pm 0.4
Ex. 7	0.061 \pm 0.095	N.T.	N.T.	N.T.	N.T.	N.T.
doxorubicin (a known anticancer compound)	0.40 \pm 0.01	0.50 \pm 0.16	0.43 \pm 0.29	0.08 \pm 0.06	0.33 \pm 0.12	0.13 \pm 0.03

N.T. = Not tested

The anti-tumor activity of the compounds of formula I may further be demonstrated employing the athymic (T cell deficient) nude mouse model which has been and remains the standard for drug discovery and development in preclinical oncology. Utilizing this model, one can measure the ability of test compounds to inhibit the growth of human tumor xenografts growing subcutaneously (s.c.) in athymic nude mice. The histologic tumor type employed was MDA-MB-435 breast carcinoma for Ex.1 and 7 and A549 non-small cell lung carcinoma for Ex. 1-3.

MDA-MB-435 human breast carcinoma: Treatments were started 15 d post implantation (3×10^6 cells/mouse), when a mean tumor volume of approximately 45 mm³ was reached. Ex.1 and 7 were administered iv at three times per week for 3 weeks (days 15, 17, 20, 22, 24, 27, 29, and 31), at 3.3, 10, and 33 μ mol/kg. Doxorubicin was administered iv at 2 mg/kg using the same schedule. Each data point represents tumor growth (mean \pm SEM), or body weight (mean), with an initial group size of n = 8, from a representative experiment performed twice. An asterisk (*) indicates p < 0.05 using a one-tailed Student's t-test.

A549 non-small cell lung carcinoma: Treatments were started 17 d post-implantation (1×10^7 cells/mouse), when a mean tumor volume of approximately 120 mm^3 was reached. Ex. 1-3 were administered iv on days 17-21 (followed by 2 d rest, then a second cycle of treatment on days 24-28). Total daily doses of 10 or $30 \text{ } \mu\text{mol/kg}$ were administered as a single injection. Data in this table were recorded on day 24, 3 d after the last treatment of the first cycle. An asterisk (*) indicates $p < 0.05$ using a one-tailed Student's t-Test.

Toxicity was monitored by recording average group body weights twice weekly, and by daily observation of general health. Efficacy was monitored by taking measurements of tumor length, width, and depth weekly using digital calipers coupled to automated data collectors. Mean tumor volume (MTV) at initiation of therapy was subtracted from final MTV in order to express the actual tumor growth during treatment (ΔMTV). Anti-tumor activity was expressed as %T/C (ΔMTV of treated group $\div \Delta \text{MTV}$ of control group $\times 100\%$). Statistical significance was evaluated using a one-tailed Student's t-test ($p < 0.05$).

The following results were obtained for compounds Ex.1 and 7 tested against MDA-MB-435 tumor xenografts 3X/week for 3 weeks:

Compound	Dose ($\mu\text{mol/kg}$)	ΔMTV (mm^3)	%T/C	Dead/Total
Ex.1	3.3	132	74*	0/8
Ex.1	10	162	90	0/8
Ex.1	33	79	44*	0/8
Ex. 7	3.3	165	102	0/8
Ex. 7	10	103	64	0/8
Ex. 7	33	48	30*	0/8
doxorubicin	2 mg/kg	82	46*	0/8

* %T/C values were statistically significant ($p < 0.05$; Student's t-test).

The following results were obtained for compounds Ex.1-3 tested against A549 tumor xenografts 5X/week for 2 weeks:

<u>Compound</u>	Dose ($\mu\text{mol/kg}$)	Δ MTV (mm^3)	%T/C	Dead/Total
Ex.1	10	95	73	0/8
Ex.1	30	39	30*	0/8
Ex.2	10	42	32*	0/8
Ex.2	30	60	46*	0/8
Ex.3	10	106	82	0/8
Ex.3	30	55	42*	0/8

* %T/C values were statistically significant ($p < 0.05$; Student's t-test).

The precise dosage of the compounds of formula I to be employed for inhibiting tumors depends upon several factors including the host, the nature and the severity of the condition being treated, the mode of administration and the particular compound employed. However, in general, satisfactory inhibition of tumors is achieved when a compound of formula I is administered parenterally, *e.g.*, intraperitoneally, intravenously, intramuscularly, subcutaneously, intratumorally, or rectally, or enterally, *e.g.*, orally, preferably intravenously or orally, more preferably intravenously at a daily dosage of 1-300 mg/kg body weight or, for most larger primates, a daily dosage of 50-5000, preferably 500-3000 mg. A preferred intravenous daily dosage is 1-75 mg/kg body weight or, for most larger primates, a daily dosage of 50-1500 mg. A typical intravenous dosage is 20 mg/kg, three to five times a week.

Usually, a small dose is administered initially and the dosage is gradually increased until the optimal dosage for the host under treatment is determined. The upper limit of dosage is that imposed by side effects and can be determined by trial for the host being treated.

The compounds of formula I may be combined with one or more pharmaceutically acceptable carriers and, optionally, one or more other conventional pharmaceutical adjuvants and administered enterally, *e.g.* orally, in the form of tablets, capsules, caplets, *etc.* or parenterally,

e.g., intraperitoneally or intravenously, in the form of sterile injectable solutions or suspensions. The enteral and parenteral compositions may be prepared by conventional means.

The compounds of formula I may be formulated into enteral and parenteral pharmaceutical compositions containing an amount of the active substance that is effective for inhibiting tumors, such compositions in unit dosage form and such compositions comprising a pharmaceutically acceptable carrier.

The following examples show representative compounds encompassed by this invention and their synthesis. However, it should be clearly understood that it is for purposes of illustration only.

EXAMPLE 1

(2*R*, 3*R*, 4*S*, 5*R*, 6*E*)-3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[(3*S*, 6*R*)-hexahydro-2-oxo-6-([decyloxy]carbonyloxy)-2*H*-azepin-3-yl]non-6-enonamide

a) Preparation of (3*S*, 6*R*)-3-(*tert*-butoxycarbonyl)aminohexahydro-6-*tert*-butyldimethylsilyloxy-2*H*-azepin-2-one.

(3*S*, 6*R*)-3-(*tert*-butoxycarbonyl)aminohexahydro-6-hydroxy-2*H*-azepin-2-one (25 g, 102 mmol), *tert*-butyldimethylsilyl chloride (23.16 g, 153 mmol), and imidazole (10.45 g, 153 mmol) are combined with 60 mL of DMF. The reaction is stirred at room temperature overnight. The mixture is diluted with 1 L of water. The resulting mixture is extracted with a 1:1 (2 x 200 mL) mixture of ethyl acetate and hexane. All organic layers are combined, washed with brine solution, dried with NaSO₄, and concentrated. The residue is purified by recrystallization with ethyl acetate/hexane to give 28.5 g (78%) of (3*S*, 6*R*)-3-(*tert*-butoxycarbonyl)aminohexahydro-6-*tert*-butyldimethylsilyloxy-2*H*-azepin-2-one as a white solid: ¹H NMR (CDCl₃) δ 5.86 (d, J=6 Hz, 1H), 5.58 (t, J=6 Hz, 1H), 4.18 (m, 1H), 3.91 (s, 1H), 3.35(dd, J=6 Hz and 16 Hz, 1H), 3.07 (m, 1H), 1.80 (m, 4H), 1.40 (s, 9H), 0.83 (s, 9H), 0.004 (s, 6H).

- b) Preparation of (3*S*, 6*R*)-3-aminohexahydro-6-*tert*-butyldimethylsilyloxy-2*H*-azepin-2-one.

(3*S*, 6*R*)-3-(*tert*-butoxycarbonyl)aminohexahydro-6-*tert*-butyldimethylsilyloxy-2*H*-azepin-2-one (8.0 g, 22 mmol) is dissolved in 40 mL of CH₂Cl₂ and cooled to -78 °C. Trimethylsilyl iodide (3.5 mL, 24.5 mmol) is added slowly. The mixture is allowed to react at -78 °C for 30 min. The reaction is warmed to 0 °C and stirred for 15 min. The solution turned yellow. The reaction is quenched with NH₄HCO₃ (3.43 g, 44 mmol) dissolved in 30 mL of CH₃OH, and 15 mL water. The mixture is concentrated and chromatographed with a 95:5 mixture of CH₂Cl₂ and methanol to yield 5.45 g (96%) of (3*S*, 6*R*)-3-aminohexahydro-6-*tert*-butyldimethylsilyloxy-2*H*-azepin-2-one as a white solid: ¹H NMR (CDCl₃) δ 5.61 (s, 1H), 3.88 (s, 1H), 3.42 (d, J=8 Hz, 1H), 3.32 (dd, J=6 Hz and 16 Hz, 1H), 3.06 (m, 1H), 1.87 (m, 2H), 1.76 (m, 1H), 1.65 (s, 3H), 0.83 (s, 9H), 0.001 (s, 6H).

- c) Preparation of (2*R*, 3*R*, 4*S*, 5*R*, 6*E*)-3,5-(methylethylidene)-3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[(3*S*, 6*R*)-hexahydro-2-oxo-6-*tert*-butyldimethylsilyloxy-2*H*-azepin-3-yl]non-6-enonamide.

(3*S*, 6*R*)-3-aminohexahydro-6-*tert*-butyldimethylsilyloxy-2*H*-azepin-2-one (5.45 g, 21 mmol), (6*E*)-6,7,8,9-tetradecoxy-8,8-dimethyl-2-*O*-methyl-3,5-*O*-(1-methylethylidene)-*gulo*-non-6-enonic acid lactone (3.0 g, 11 mmol), and diisopropylethylamine (4.6 mL, 26 mmol) are combined with 30 mL of isopropanol at room temperature. The mixture is heated to reflux overnight. The mixture is cooled to room temperature and concentrated. The residue is chromatographed with a 98:2 mixture of CH₂Cl₂ and methanol to yield 2.53 g (42%) of (2*R*, 3*R*, 4*S*, 5*R*, 6*E*)-3,5-(methylethylidene)-3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[(3*S*, 6*R*)-hexahydro-2-oxo-6-*tert*-butyldimethylsilyloxy-2*H*-azepin-3-yl]non-6-enonamide (42%) as a white solid: ¹H NMR (CDCl₃) δ 7.53 (d, J=6 Hz, 1H), 5.72 (d, J=16 Hz, 1H), 5.47 (dd, J=6 Hz and 16 Hz, 1H), 4.47 (m, 1H), 4.22 (d, J=6 Hz, 1H), 4.03 (d, J=8 Hz, 1H), 3.91 (m, 1H), 3.82 (d, J=7 Hz, 1H), 3.48 (d, J=9 Hz, 1H), 3.43 (s, 3H), 3.35 (d, J=6 Hz, 1H), 3.09 (m, 1H), 2.77 (d, J=9 Hz, 1H), 1.83 (m, 2H), 1.77 (m, 2H), 1.41 (d, J=6 Hz, 6H), 0.97 (s, 9H), 0.83 (s, 9H), 0.005 (s, 6H); ¹³C NMR (CDCl₃) δ 172.2, 169.6, 148.3, 145.3, 121.5, 108.8, 99.6, 81.4, 80.5, 79.2, 78.2, 74.4, 73.1, 69.1, 67.9, 65.8, 59.2, 56.4, 51.7, 36.8, 36.5, 33.1, 29.6, 29.4, 19.1.

- d) Preparation of (2*R*, 3*R*, 4*S*, 5*R*, 6*E*)-3,5-(methylethylidene)-3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[(3*S*, 6*R*)-hexahydro-2-oxo-6-hydroxy-2*H*-azepin-3-yl]non-6-enonamide.

(2*R*, 3*R*, 4*S*, 5*R*, 6*E*)-3,5-(methylethylidene)-3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[(3*S*, 6*R*)-hexahydro-2-oxo-6-*tert*-butyldimethylsilyloxy-2*H*-azepin-3-yl]non-6-enonamide (2.5 g, 4.6 mmol) is dissolved in 30 mL of THF. 1.0 M in THF solution of tetra-*n*-butylammonium fluoride (13.8 mL, 14 mmol) is added at room temperature and stirred for 3 h. The mixture is concentrated and chromatographed with a 95:5 mixture of CH₂Cl₂ and methanol to give 1.8 g (91%) of (2*R*, 3*R*, 4*S*, 5*R*, 6*E*)-3,5-(methylethylidene)-3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[(3*S*, 6*R*)-hexahydro-2-oxo-6-hydroxy-2*H*-azepin-3-yl]non-6-enonamide as a white solid: ¹H NMR (CDCl₃) δ 7.61 (d, J=6 Hz, 1H), 6.45 (t, J=6 Hz, 1H), 5.77 (d, J=6 Hz, 1H), 5.52 (dd, J=6 Hz, and 16 Hz, 1H), 4.56 (m, 1H), 4.28 (d, J=6 Hz, 1H), 4.06 (d, J=8 Hz, 1H), 4.00 (m, 1H), 3.91 (d, J=8 Hz, 1H), 3.54 (m, 1H), 3.47 (s, 3H), 3.35 (m, 2H), 3.08 (d, J=8 Hz, 1H), 2.76 (d, J=6 Hz, 1), 2.02 (m, 2H), 1.83 (m, 2H), 1.45 (s, 6H), 1.03 (s, 9H); ¹³C NMR (CDCl₃) δ 175.1, 169.7, 145.3, 121.5, 99.7, 83.1, 80.6, 74.5, 73.2, 65.8, 64.6, 59.1, 51.8, 45.9, 34.5, 33.1, 29.5, 29.3, 25.1, 19.1, 13.7.

- e) Preparation of (2*R*, 3*R*, 4*S*, 5*R*, 6*E*)-3,5-(methylethylidene)-3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[(3*S*, 6*R*)-hexahydro-2-oxo-6-([decyloxy]carbonyloxy)-2*H*-azepin-3-yl]non-6-enonamide.

Decyl chloroformate (0.68 g, 2.8 mmol), triethylamine (0.4 mL, 2.8 mmol), and DMAP (0.11 g, 0.9 mmol) are added sequentially to a stirred solution consisting of (2*R*, 3*R*, 4*S*, 5*R*, 6*E*)-3,5-(methylethylidene)-3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[(3*S*, 6*R*)-hexahydro-2-oxo-6-hydroxy-2*H*-azepin-3-yl]non-6-enonamide (0.8 g, 1.9 mmol) and CH₂Cl₂ (20 mL) at 0 °C. The mixture is allowed to warm to room temperature and then is stirred for 72 h. The mixture is concentrated. The residue is chromatographed with a 98:2 mixture of CH₂Cl₂ and methanol to give 0.52 g (46%) of (2*R*, 3*R*, 4*S*, 5*R*, 6*E*)-3,5-(methylethylidene)-3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[(3*S*, 6*R*)-hexahydro-2-oxo-6-([decyloxy]carbonyloxy)-2*H*-azepin-3-yl]non-6-enonamide as a white solid: ¹H NMR (CDCl₃) δ 7.58 (d, J = 6 Hz, 1H), 5.80 (d, J = 16 Hz, 1H), 5.65 (m, 1H), 5.53 (dd, J = 16 Hz and 6 Hz, 1H), 4.78 (m, 1H), 4.58 (m, 1H), 4.22 (d, J = 7 Hz, 1H), 4.09 (m, 2H), 4.03 (d, J = 7 Hz, 1H), 3.85 (d, J = 7 Hz, 1H), 3.57 (m, 3H), 3.45 (s, 3H), 2.25

(m, 1H), 1.90 (m, 4H), 1.68 (m, 1H), 1.45 (d, J = 5 Hz, 6H), 1.30 (m, 15 H), 1.05 (s, 9H), 0.94 (m, 3H).

f) Preparation of the title compound.

A 30 mL solution of (3:3:2) TFA, THF, and water at 0 °C is added to a flask containing (2*R*, 3*R*, 4*S*, 5*R*, 6*E*)-3,5-(methylethylidene)-3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[(3*S*, 6*R*)-hexahydro-2-oxo-6-([decyloxy]carbonyl)oxy)-2*H*-azepin-3-yl]non-6-enonamide (0.52 g, 0.85 mmol). The mixture is allowed to react at 0 °C for 30 min. The mixture is evaporated to dryness *in vacuo*. The residue is neutralized with a solution of NH₄HCO₃ (1.2 g in 20 mL of water). The mixture is evaporated to dryness under high vacuum. The residue is chromatographed with a 95:5 mixture of CH₂Cl₂ and methanol to yield 0.2 g (41%) of the title compound as a white solid: ¹H NMR (CDCl₃) δ 8.04 (d, J = 6 Hz, 1H), 5.85 (m, 2H), 5.44 (dd, J = 16 Hz and 7 Hz, 1H), 4.84 (m, 1H), 4.57 (m, 1H), 4.25 (m, 2H), 4.14 (m, 2H), 3.83 (m, 2H), 3.63 (m, 2H), 3.56 (s, 3H), 3.54 (m, 1H), 3.25 (m, 1H), 3.08 (br s, 1H), 2.3 (m, 1H), 2.01 (m, 3H), 1.68 (m, 3H), 1.33 (m, 15 H), 1.05 (s, 9H), 0.91 (t, J = 6 Hz, 3H); ¹³C NMR (CDCl₃) δ 173.9, 172.4, 154.7, 145.9, 123.4, 81.2, 74.7, 73.0, 70.8, 68.8, 60.2, 51.8, 43.6, 33.2, 32.1, 32.0, 31.5, 29.7, 29.5, 29.4, 28.8, 25.9, 25.7, 22.9, 14.3.

EXAMPLE 2

(2*R*, 3*R*, 4*S*, 5*R*, 6*E*)-3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[(3*S*, 6*R*)-hexahydro-2-oxo-6-([pentyloxy]carbonyl)oxy)-2*H*-azepin-3-yl]non-6-enonamide

a) Preparation of 3,5:6,7-*bis-O*-(1-methylethylidene)-α-D-glucoheptonic γ-lactone.

α-D-Glucoheptonic γ-lactone (500 g, 2.4 mol) is added into 9 L of acetone in a 5 gal plastic drum. The mixture is agitated mechanically until most of the solid dissolved (15-20 min). Iodine (60 g, 0.236 mol) is added portionwise into the lactone solution over 5-10 min. The resulting mixture is stirred overnight. A saturated solution of Na₂S₂O₃ (1.3 L) is added to the iodine solution to quench the reaction. The resulting solution is concentrated to about half of its original volume *in vacuo*, and brine soln (5 L) is added. The resulting mixture is extracted with 3 x 1.2 L EtOAc. All

organic layers are combined and evaporated to dryness. The solid is slurried with a mixture of ether and hexane (3:7), and filtered. The filter cake is washed with Et₂O (50 mL) and air dried, giving 599 g of the desired compound as a white powder (86.5%): ¹H NMR (CDCl₃) δ 4.62 (m, 1H), 4.50 (m, 1H), 4.35 (m, 2H), 4.07 (m, 1H), 3.93 (m, 1H), 3.82 (dd, 1H), 3.08 (d, 1H), 1.51 (s, 3H), 1.44 (s, 3H), 1.39 (s, 3H), 1.35 (s, 3H); ¹³C NMR (CDCl₃) δ 174.4, 109.4, 98.6, 72.8, 71.4, 69.3, 68.4, 67.8, 66.7, 28.6, 26.7, 24.6, 19.3.

b) Preparation of 2-*O*-methyl-3,5:6,7-*bis-O*-(1-methylethylidene)-α-D-glucoheptonic γ-lactone.

3,5:6,7-*bis-O*-(1-methylethylidene)-α-D-glucoheptonic γ-lactone (719 g, 2.49 mol) is added into 4.5 L of CH₂Cl₂ in a 5 gal plastic drum. The mixture is stirred under N₂. Iodomethane (2500 g, 17.6 mol) is added immediately followed by addition of silver(I)oxide (1750 g, 7.58 mol). Water (30 mL) is added to the reaction mixture. An ice bath is used to maintain the reaction temperature at 15-30 °C. The reaction is stirred in the absence of light for 18 h. After diluting the reaction mixture with 1.5 L of CH₂Cl₂, the solid is filtered and washed with an additional 2.2 L of CH₂Cl₂. The undesired solid is discarded and the filtrate is evaporated to dryness. The residue is slurried in Et₂O (1.5 L), filtered, and dried to give 618 g product (82 %): ¹H NMR (CDCl₃) δ 4.75 (m, 1H), 4.33 (m, 1H), 4.29 (m, 1H), 4.15 (m, 1H), 4.07 (m, 1H), 3.96 (dd, 1H), 3.83 (dd, 1H), 3.65 (s, 3H), 1.57 (s, 3H), 1.42 (s, 6H), 1.35 (s, 3H); ¹³C NMR (CDCl₃) δ 172.5, 109.6, 98.5, 79.0, 73.1, 69.5, 68.6, 67.5, 66.9, 59.1, 28.9, 26.9, 24.9, 19.4.

c) Preparation of 2-*O*-Methyl-3,5-*O*-(1-methylethylidene)-α-D-glucoheptonic γ-lactone.

2-*O*-methyl-3,5:6,7-*bis-O*-(1-methylethylidene)-α-D-glucoheptonic γ-lactone (618 g, 2.05 mol) is dissolved in 8 L of a mixture of acetic acid and water (1:1) over 30 min. The solution is stirred at ambient temperature overnight. The solution is evaporated to dryness *in vacuo*. The solid is slurried in 3-5 L of hot acetone and filtered. After oven drying at 20-30 °C, 363 g of the desired compound is obtained (67.6 %). ¹H NMR(CDCl₃): δ 4.92 (d, 1H), 4.80 (m, 1H), 4.47 (d, 1H), 4.42 (t, 1H), 4.39 (m, 1H), 3.95 (dd, 1H), 3.75 (m, 2H), 3.4 (s, 3H), 2.5 (m, 1H), 1.42 (s, 3H), 1.22 (s, 3H).

d) Preparation of 2,4-*O*-(1-methylethylidene)-5-*O*-methyl-L-glucuronic γ - lactone.

2-*O*-Methyl-3,5-*O*-(1-methylethylidene)- α -D-glucoheptonic γ - lactone (200 g, 0.76 mol) is dissolved into a 1:1 mixture of methanol and water (3.6 L). The stirred mixture is cooled in an ice water bath to about 8 °C. Solid NaIO₄ (213 g, 0.98 mol) is added portionwise. Reaction is complete within 40 min as indicated by TLC (silica gel, 5% methanol, 15% EtOAc in CH₂Cl₂). Solid NaCl is added into the reaction mixture to saturate the methanolic solution. The solid is filtered and washed with 2 L CH₂Cl₂. The filtrate is extracted with 7x500 mL CH₂Cl₂. Combined organic layers are dried over Na₂SO₄, filtered and concentrated to a syrup, which formed a precipitate upon addition of hexane. The solid is filtered and rinsed with Et₂O. A portion of the crude product (50 g) is dissolved in 3 L CHCl₃ and heated to reflux. After rotary evaporation of 2.1 L of CHCl₃ at atmospheric pressure (methanol is driven out of the system by coevaporation with CHCl₃) the residue is evaporated to dryness. 44 g of the desired product is obtained as a solid after drying *in vacuo* overnight. ¹H NMR (CDCl₃): δ 9.60 (s, 1H), 4.78 (m, 1H), 4.42 (s, 2H), 4.15 (dd, 1H), 3.65 (s, 3H), 1.58 (s, 3H), 1.55 (s, 3H); ¹³C NMR (CDCl₃) δ 198.8, 171.9, 99.0, 78.4, 74.4, 72.9, 68.4, 67.4, 59.2, 28.7, 19.0.

e) Preparation of (6*E*)-6,7,8,9-tetradecoxy-8,8-dimethyl-2-*O*-methyl-3,5-*O*-(1-methylethylidene)-*gulo*-non-6-enonic acid lactone.

Into a 2 L round bottom flask, is added CrCl₂ (50 g, 41 mmol), anhydrous THF (750 mL), and DMF (32 mL). The mixture is stirred under N₂ for 1h. A solution of 2,4-*O*-(1-methylethylidene)-5-*O*-methyl-L-glucuronic γ - lactone (12 g, 50 mmol), 1,1-diiodo-2,2-dimethylpropane (15 mL), and 500 mL of anhydrous THF is added slowly into the reaction mixture. After the addition, the reaction mixture is stirred at ambient temp for 1.5 h. The reaction is quenched with satd. aq. NH₄Cl. The residue is partitioned between EtOAc/water and chromatographed (5% EtOAc - CH₂Cl₂) to give 9 g (63%) of the desired compound as a white crystalline solid: ¹H NMR (CDCl₃) δ 5.82 (d, 1H), 5.58 (q, 1H), 4.71 (m, 1H), 4.46 (m, 1H), 4.10 (dd, 1H), 4.0 (m, 1H), 3.66 (s, 3H), 1.58 (s, 3H), 1.53 (s, 3H), 1.07 (s, 9H); ¹³C NMR (CDCl₃) δ 172.5, 147.0, 120.2, 98.7, 79.1, 71.9, 70.3, 67.6, 59.2, 33.2, 29.3, 19.3.

- f) Preparation of (3*S*, 6*R*)-3-(*tert*-butoxycarbonyl)aminohexahydro-6-hydroxy-2*H*-azepin-2-one.

To a 1 L flask containing 500 ml DMF, (5*R*)-5-hydroxy-L-lysine (10 g, 0.040 mol), 1-hydroxybenzotriazole hydrate (8.2 g, 0.060 mol) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide·HCl (11.6 g, 0.060 mol) are added. After 0.5 h, triethylamine (16.8 ml, 0.120 mol) is added. The reaction is stirred at rt for 48 h. Di-*tert*-butyl dicarbonate (17.6 g, 0.080 mol) and triethylamine (16.8 ml, 0.120 mol) are added. Stirring is continued for 16 h. The reaction mixture is filtered to remove triethylamine·HCl and the solvent is removed by rotary evaporation under high vacuum to give a thick oil. The oil is dissolved in 150 ml CH₂Cl₂ and applied to a silica gel column (150 g, 40 x 250 mm). The column is eluted with 3% methanol in CH₂Cl₂ to give the crude product as a solid. The crude solid is dissolved in 120 ml hot CH₂Cl₂ and cooled to -20 °C for 1 h. The resulting solid is filtered and washed with 50 ml CH₂Cl₂. The combined filtrates are evaporated to dryness. CH₂Cl₂ (40 ml) is added to this residue and the resulting slurry is stirred for 0.5 h at rt. The slurry is filtered and the solid washed with 25 ml CH₂Cl₂. The solids are combined to give 5.57 g of (3*S*, 6*R*)-3-(*tert*-butoxycarbonyl)aminohexahydro-6-hydroxy-2*H*-azepin-2-one. 300 MHz ¹H NMR (DMSO) δ 7.42 (1 H, t, J = 5.1 Hz), 6.38 (1 H, d, J = 6.6 Hz), 4.60 (1 H, d, J = 4.2 Hz), 4.07 (1 H, m), 3.74 (1 H, m), 3.32 (1 H, m), 3.03 (1 H, m), 1.8-1.5 (4 H, m), 1.39 (9 H, s).

- g) Preparation of (3*S*, 6*R*)-3-(*tert*-butoxycarbonyl)aminohexahydro-6-([pentyloxy]carbonyloxy)-2*H*-azepin-2-one.

Triethylamine (2 mL, 15 mmol) is added to a solution of pentyl chloroformate (1.8 g, 12.2 mmol), (3*S*, 6*R*)-3-(*tert*-butoxycarbonyl)aminohexahydro-6-hydroxy-2*H*-azepin-2-one (1.5 g, 6.1 mmol) and 20 mL of CH₂Cl₂ at 5 °C. The reaction mixture is stirred at room temperature overnight. The reaction mixture is then partitioned with water, and the organic layer is dried (Na₂SO₄), and concentrated by rotary evaporation. The resulting residue is chromatographed (5% EtOAc - CH₂Cl₂) to give 1.3 g (60%) of (3*S*, 6*R*)-3-(*tert*-butoxycarbonyl)aminohexahydro-6-([pentyloxy]carbonyloxy)-2*H*-azepin-2-one as a pale yellow solid: ¹H NMR (CDCl₃): δ 5.90 (d, J

= 6 Hz, 1H), 5.77 (t, J = 6 Hz, 1H), 4.79 (m, 1H), 4.30 (m, 1H), 4.12 (m, 3H), 3.53 (m, 2H), 2.24 (m, 1H), 1.92 (m, 2H), 1.66 (m, 1H), 1.44 (s, 9H), 1.34 (m, 5H), 0.91 (m, 3H).

h) Preparation of (3*S*, 6*R*)-3-aminohexahydro-6-([pentyloxy]carbonyloxy)-2*H*-azepin-2-one.

To a solution of (3*S*, 6*R*)-3-(*tert*-butoxycarbonyl)aminohexahydro-6-([pentyloxy]carbonyloxy)-2*H*-azepin-2-one (1.3 g, 3.6 mmol) in 40 mL of CH₂Cl₂ is added TFA (25 mL) at room temperature, and the reaction solution is stirred at room temperature for 1 h, then concentrated via rotary evaporation (bath temp <20 °C). The residue is diluted with CH₂Cl₂ (100 mL), and washed with NH₄OH (10 mL) and then water (2x20mL) and dried (Na₂SO₄). The reaction mixture is adsorbed on silica and chromatographed (5% methanol-CH₂Cl₂) to give 0.6 g (64.0%) of (3*S*, 6*R*)-3-aminohexahydro-6-([pentyloxy]carbonyloxy)-2*H*-azepin-2-one as a white solid: ¹H NMR (CDCl₃): δ 4.31 (m, 1H), 4.12 (m, 2H), 3.58 (br s, 1H), 3.34 (m, 5H), 2.06 (m, 2H), 1.66 (m, 2H), 1.33 (m, 5H), 0.92 (m, 3H).

i) Preparation of (2*R*, 3*R*, 4*S*, 5*R*, 6*E*)-3,5-(methylethylidene)-3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[(3*S*, 6*R*)-hexahydro-2-oxo-6-([pentyloxy]carbonyloxy)-2*H*-azepin-3-yl]non-6-enonamide.

A solution consisting of (3*S*, 6*R*)-3-aminohexahydro-6-([pentyloxy]carbonyloxy)-2*H*-azepin-2-one (0.6 g, 2.3 mmol) and ether (5 mL) is treated with HCl (6 mL of 1 M solution in ether). The mixture is stirred until a white precipitate forms. The precipitate is filtered and added to a solution consisting of (6*E*)-6,7,8,9-tetradecoxy-8,8-dimethyl-2-*O*-methyl-3,5-*O*-(1-methylethylidene)-*gulo*-non-6-enonic acid lactone (0.5 g, 1.8 mmol), sodium 2-ethylhexanoate (0.4 g, 2.6 mmol), 2-hydroxypyridine (0.05 g, 0.54 mmol) and ethyl acetate (10 mL). The reaction is stirred at room temperature for 72 h. The reaction mixture is adsorbed on silica and chromatographed (2% methanol - CH₂Cl₂) to give 0.47 g (49%) of the desired compound as a pale yellow solid: ¹H NMR (CDCl₃) δ 7.56 (d, J = 6 Hz, 1H), 5.81 (s, 1H), 5.75 (m, 2H), 5.53 (m, 2H), 4.81 (m, 1H), 4.60 (m, 1H), 4.28 (m, 2H), 4.11 (m, 4H), 3.91 (dd, J = 13 Hz and 7 Hz, 2H), 3.54 (s, 3H), 2.25 (m, 1H), 2.03 (m, 2H), 1.83 (m, 1H), 1.66 (m, 2H), 1.45 (m, 7H), 1.35 (m, 2H), 1.04 (s, 9H), 0.93 (m, 3H).

j) Preparation of the title compound.

(2*R*, 3*R*, 4*S*, 5*R*, 6*E*)-3,5-(methylethylidene)-3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[(3*S*, 6*R*)-hexahydro-2-oxo-6-([pentyloxy]carbonyl)oxy)-2*H*-azepin-3-yl]non-6-enonamide (0.47 g, 0.86 mmol) is added in one portion to a stirred solution of TFA (10 mL), THF (10 mL), and water (5 mL) at 0 °C. The reaction is stirred at this temp for 30 min, concd via rotary evaporation (bath temp <20 °C), mixed with saturated NH₄HCO₃ (5 mL), and stirred for 15 min. The mixture is concentrated *in vacuo* and chromatographed (2% methanol - CH₂Cl₂) to give a white solid. This material is further purified using preparative hplc (reverse phase eluted with 90% CH₃CN - water) to give 0.2 g (46%) of the title compound as a white solid: ¹H NMR (CDCl₃) δ 8.02 (d, *J* = 6 Hz, 1H), 5.83 (m, 2H), 5.42 (dd, *J* = 16 Hz and 7 Hz, 1H), 4.82 (m, 1H), 4.55 (m, 1H), 4.24 (m, 1H), 4.12 (t, *J* = 8 Hz, 2H), 3.81 (m, 2H), 3.61 (m, 2H), 3.55 (s, 3H), 3.30 (m, 2H), 2.28 (m, 1H), 2.00 (m, 2H), 1.64 (m, 3H), 1.35 (m, 5H), 1.02 (s, 9H), 0.92 (t, *J* = 7 Hz, 3H); ¹³C NMR (CDCl₃) δ 174.1, 172.6, 154.8, 146.2, 123.6, 81.4, 74.9, 73.1, 72.8, 70.9, 68.9, 60.3, 51.9, 43.8, 33.4, 32.2, 29.8, 28.7, 28.2, 25.8, 22.7, 14.3.

EXAMPLE 3

Preparation of (2*R*, 3*R*, 4*S*, 5*R*, 6*E*)-3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[(3*S*, 6*R*)-hexahydro-2-oxo-6-([2-phenylethoxy]carbonyl)oxy)-2*H*-azepin-3-yl]non-6-enonamide.

Following essentially the procedure of Example 2g) and using in place of pentyl chloroformate, an approximately equivalent amount of 2-phenylethoxychloroformate, (3*S*, 6*R*)-3-(*tert*-butoxycarbonyl)aminohexahydro-6-([2-phenylethoxy]carbonyl)oxy)-2*H*-azepin-2-one is obtained. Employing the latter compound in place of compound 2g), and following essentially the procedure of Example 2h), 2i) and the last step of Example 2, the title compound is obtained. ¹H NMR (CDCl₃): δ 8.03 (d, *J* = 6 Hz, 1H), 7.35 (m, 2H), 7.27 (m, 3H), 5.85 (d, *J* = 16 Hz, 1H), 5.75 (t, *J* = 5.5 Hz, 1H), dd (*J* = 16 Hz and 7 Hz, 1H), 4.80 (m, 1H), 4.55 (m, 1H), 4.39 (m, 2H), 4.24 (m, 2H), 3.83 (m, 2H), 3.63 (m, 1H), 3.57 (s, 3H), 3.55 (m, 2H), 3.25 (d, *J* = 7 Hz, 1H), 3.07 (d, *J* = 2 Hz, 1H), 3.01 (t, *J* = 7 Hz, 2H), 2.25 (m, 1H), 1.97 (m, 3H), 1.05 (s, 9H); ¹³C NMR (CDCl₃): δ 174.1,

172.6, 154.6, 146.2, 137.4, 129.4, 129.0, 127.2, 123.6, 81.4, 74.9, 73.1, 72.8, 71.1, 68.9, 60.4, 51.9, 43.6, 35.5, 33.4, 32.2, 29.8, 26.1.

EXAMPLE 4

Preparation of (2*R*, 3*R*, 4*S*, 5*R*, 6*E*)-3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[(3*S*, 6*R*)-hexahydro-2-oxo-6-([phenylmethoxy]carbonyl)oxy)-2*H*-azepin-3-yl]non-6-enonamide.

Following essentially the procedure of Example 1e) and using in place of decyl chloroformate, an approximately equivalent amount of benzyl chloroformate, (3*S*, 6*R*)-3-(*tert*-butoxycarbonyl)aminohexahydro-6-([phenylmethoxy]carbonyl)oxy)-2*H*-azepin-2-one is obtained. Employing the latter compound in place of compound 1f), and following essentially the procedure of Example 1h), 1i) and the last step of Example 1, the title compound is obtained. ¹H NMR (CDCl₃) δ 8.01 (d, J = 6 Hz, 1H), 7.39 (m, 5H), 5.88 (t, J = 7 Hz, 1H), 5.84 (d, J = 15 Hz, 1H), 5.43 (dd, J = 15 Hz and 1 Hz, 1H), 5.17 (s, 2H), 4.85 (m, 1H), 4.55 (m, 1H), 4.23 (m, 2H), 3.83 (m, 2H), 3.62 (m, 2H), 3.55 (s, 3H), 3.51 (m, 1H), 3.27 (d, J = 8 Hz, 1H), 3.09 (d, J = 3 Hz, 1H), 2.28 (m, 1H), 1.97 (m, 3H), 1.04 (s, 9H); ¹³C NMR (CDCl₃): δ 174.1, 172.5, 154.6, 146.1, 135.2, 129.2, 129.1, 128.1, 123.6, 81.5, 74.9, 73.1, 72.8, 71.4, 70.4, 69.6, 60.3, 59.7, 55.2, 44.0, 43.7, 33.4, 32.2, 29.8, 29.7, 25.8.

EXAMPLE 5

Preparation of (2*R*, 3*R*, 4*S*, 5*R*, 6*E*)-3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[(3*S*, 6*R*)-hexahydro-2-oxo-6-([2,2-dimethylpropoxy]carbonyl)oxy)-2*H*-azepin-3-yl]non-6-enonamide.

Following essentially the procedure of Example 2g) and using in place of pentyl chloroformate, an approximately equivalent amount of neopentyl chloroformate, (3*S*, 6*R*)-3-(*tert*-butoxycarbonyl)aminohexahydro-6-([2,2-dimethylpropoxy]carbonyl)oxy)-2*H*-azepin-2-one is obtained. Employing the latter compound in place of compound 2g), and following essentially the

procedure of Example 2h), 2i) and the last step of Example 2, the title compound is obtained. ^1H NMR (CDCl_3) δ 8.03 (d, $J = 6$ Hz, 1H), 5.91 (t, $J = 6$ Hz, 1H), 5.83 (dd, $J = 16$ Hz and 1 Hz, 1H), 5.42 (dd, $J = 16$ Hz and 7.5 Hz, 1H), 4.82 (m, 1H), 4.56 (m, 1H), 4.24 (m, 2H), 3.82 (m, 3H), 3.61 (m, 2H), 3.54 (s, 3H), 3.49 (s, 2H), 3.28 (m, 1H), 3.11 (br s, 1H), 2.29 (m, 1H), 1.99 (m, 3H), 1.03 (s, 9H), 0.96 (s, 9H); ^{13}C NMR (CDCl_3) δ 174.3, 172.6, 155.1, 146.2, 123.5, 81.4, 74.9, 74.6, 73.1, 72.8, 70.9, 60.4, 52.0, 51.3, 43.8, 33.4, 32.2, 31.9, 29.8, 26.7, 25.9.

EXAMPLE 6

Preparation of (2*R*, 3*R*, 4*S*, 5*R*, 6*E*)-3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[(3*S*, 6*R*)-hexahydro-2-oxo-6-([cyclohexyloxy]carbonyl)oxy)-2*H*-azepin-3-yl]non-6-enonamide.

Following essentially the procedure of Example 2g) and using in place of pentyl chloroformate, an approximately equivalent amount of cyclohexyl chloroformate, (3*S*, 6*R*)-3-(*tert*-butoxycarbonyl)aminohexahydro-6-([cyclohexyloxy]carbonyl)oxy)-2*H*-azepin-2-one is obtained. Employing the latter compound in place of compound 2g), and following essentially the procedure of Example 2h), 2i) and the last step of Example 2, the title compound is obtained. ^1H NMR (CDCl_3) δ 8.02 (d, $J = 6$ Hz, 1H), 5.87 (m, 1H), 5.83 (d, $J = 16$ Hz, 1H), 5.42 (dd, $J = 16$ Hz and 1 Hz, 1H), 4.81 (m, 1H), 4.57 (m, 2H), 4.24 (m, 2H), 3.81 (m, 2H), 3.61 (t, $J = 6$ Hz, 1H), 3.54 (s, 3H), 3.52 (s, 1H), 3.49 (m, 1H), 3.26 (d, $J = 7.5$ Hz, 1H), 3.10 (s, 1H), 2.28 (m, 1H), 1.94 (m, 3H), 1.76 (m, 2H), 1.56 (m, 1H), 1.43 (m, 2H), 1.30 (m, 5H), 1.03 (s, 9H); ^{13}C NMR (CDCl_3) δ 174.2, 172.6, 168.4, 154.2, 146.2, 123.5, 81.4, 74.9, 73.2, 72.8, 70.8, 60.4, 52.0, 43.8, 33.4, 32.0, 31.9, 29.8, 25.9, 25.5, 24.1, 23.1, 14.5.

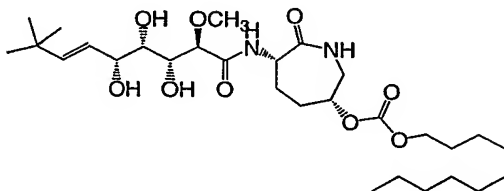
EXAMPLE 7

Preparation of (2*R*, 3*R*, 4*S*, 5*R*, 6*E*)-3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[(3*S*, 6*R*)-hexahydro-2-oxo-6-([undecyloxy]acetyl)oxy)-2*H*-azepin-3-yl]non-6-enonamide.

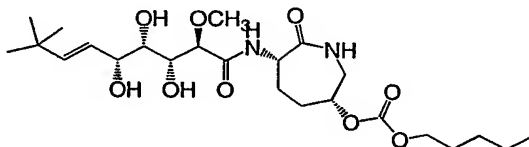
Following essentially the procedure of Example 1e) and using in place of decyl chloroformate, an approximately equivalent amount of undecyloxyacetyl chloride, (3*S*, 6*R*)-3-(*tert*-butoxycarbonyl)aminohexahydro-6-([undecyloxy]acetyl)oxy)-2*H*-azepin-2-one is obtained. Employing the latter compound in place of compound 1f), and following essentially the procedure of Example 1h), 1i) and the last step of Example 1, the title compound is obtained. ¹H NMR (CDCl₃) δ 7.92 (d, J = 7Hz, 1H), 6.69 (m, 1H), 5.85 (d, J = 16 Hz, 1H), 5.44 (dd, J = 16 Hz and 7 Hz, 1H), 4.56 (m, 1H), 4.45 (m, 1H), 4.24 (m, 1H), 4.11 (s, 2H), 4.03 (br s, 1H), 3.86 (m, 2H), 3.66 (m, 2H), 3.54 (m, 2H), 3.53 (s, 3H), 3.39 (m, 1H), 3.06 (m, 1H), 2.11 (m, 1H), 1.88 (m, 2H), 1.64 (m, 2H), 1.28 (m, 18H), 1.04 (s, 9H), 0.90 (t, J = 7 Hz, 3H); ¹³C NMR (CDCl₃): δ 175.5, 172.5, 146.2, 123.6, 82.4, 74.9, 73.2, 72.6, 68.7, 68.4, 64.9, 60.3, 52.3, 46.4, 34.9, 33.4, 32.3, 30.0, 29.7, 26.4, 25.1, 23.1, 14.5.

Following are the corresponding structures of the compounds of Examples 1-7:

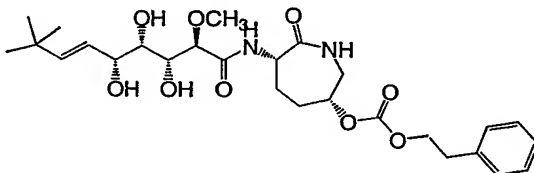
EXAMPLE 1



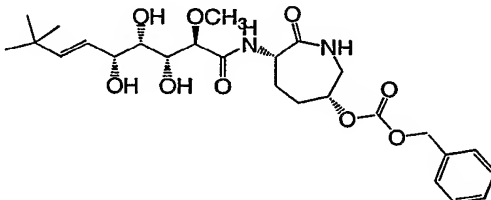
EXAMPLE 2



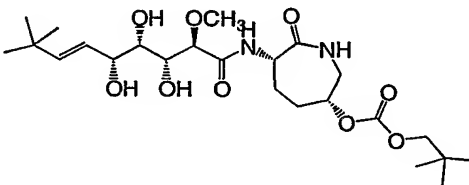
EXAMPLE 3



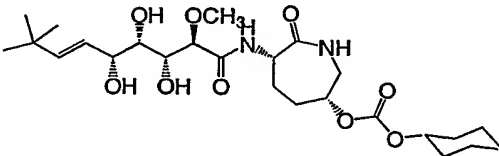
EXAMPLE 4



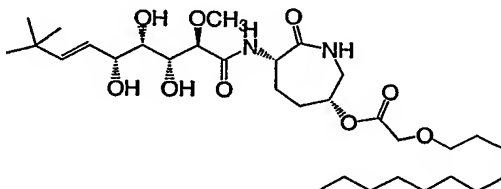
EXAMPLE 5



EXAMPLE 6

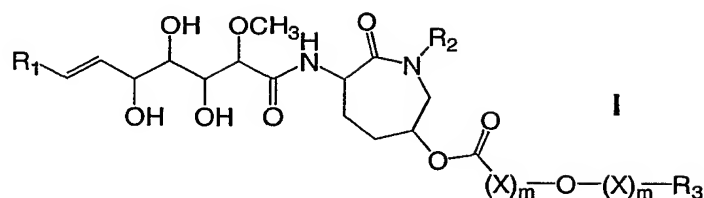


EXAMPLE 7



WHAT IS CLAIMED IS:

1. A compound of formula I:



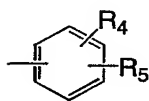
where R_1 is (C_{1-6}) alkyl or (C_{3-6}) cycloalkyl;

R_2 is hydrogen or (C_{1-6}) alkyl;

each X, independently, is (C_{1-12}) alkylene;

each m, independently, is 0 or 1;

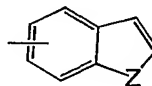
and R_3 is (C_{1-12}) alkyl; (C_{2-12}) alkenyl; (C_{2-12}) alkynyl; (C_{3-8}) cycloalkyl; or an aromatic ring system selected from II, III, IV and V:



II



III



IV



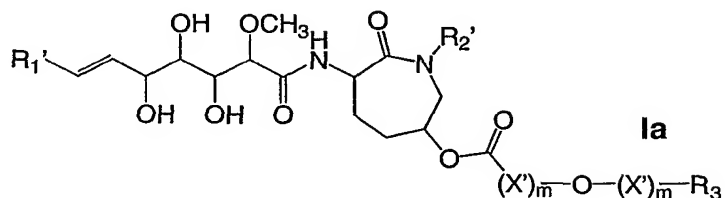
V

where R_4 is hydrogen, chloro, or methoxy; R_5 is hydrogen, chloro,

(C_{1-18}) alkyl or (C_{1-18}) alkoxy; and Z is oxygen, sulfur, N-H, or N-CH₃;

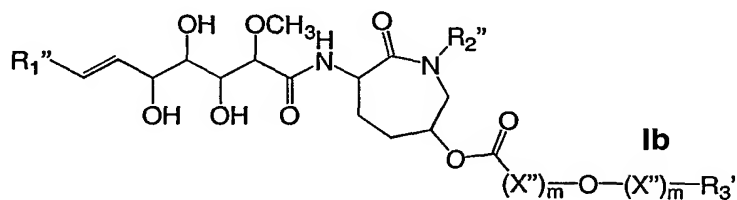
or a pharmaceutically acceptable acid addition salt thereof, where possible.

2. A compound according to Claim 1 of formula Ia:

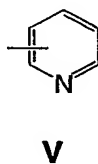
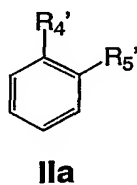


where each m , independently, and R_3 are as defined in Claim 1;
 R_1' is (C_{1-6}) alkyl;
 R_2' is hydrogen or (C_{1-4}) alkyl;
 and each X' , independently, is (C_{1-6}) alkylene;
 or a pharmaceutically acceptable acid addition salt thereof, where possible.

3. A compound according to Claim 2 of formula Ib:

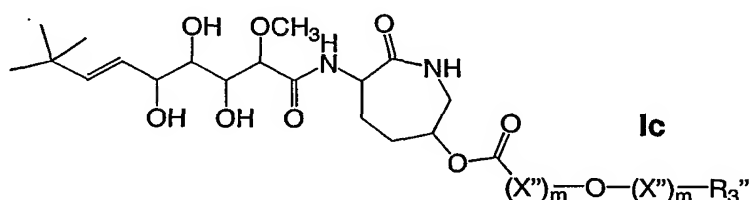


where each m , independently, is as defined in Claim 2;
 R_1'' is *i*-propyl or *t*-butyl;
 R_2'' is hydrogen or methyl;
 R_3' is (C_{1-6}) alkyl, (C_{2-6}) alkenyl, (C_{5-7}) cycloalkyl; or an aromatic ring system selected from IIa and V:



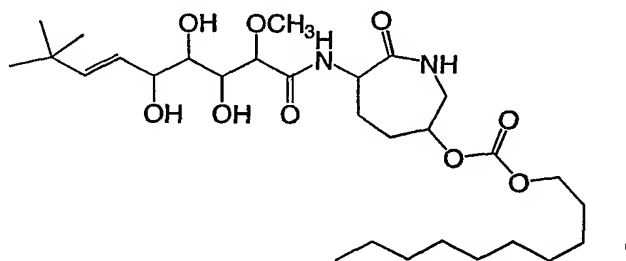
where R_4' is in the *meta* position and is hydrogen or chloro; and R_5' is in the *para* position and is hydrogen, chloro, (C_{1-18}) alkyl or (C_{1-18}) alkoxy;
and each X'' , independently, is (C_{1-6}) alkylene;
or a pharmaceutically acceptable acid addition salt thereof, where possible.

4. A compound according to Claim 3 of formula Ic:

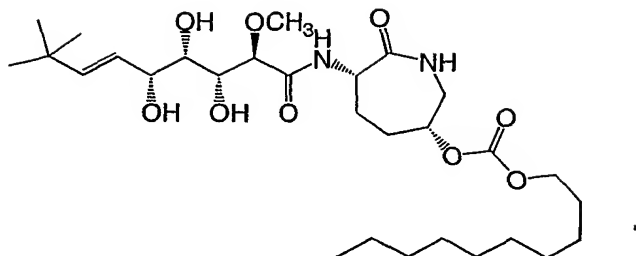


where each m and each X'' , independently, are as defined in Claim 3; and
 R_3'' is (C_{1-6}) alkyl, (C_{5-7}) cycloalkyl, phenyl, 3,4-dichlorophenyl, 4-methoxyphenyl, 4-*n*-decylphenyl, 4-*n*-decyloxyphenyl or 3-pyridyl.

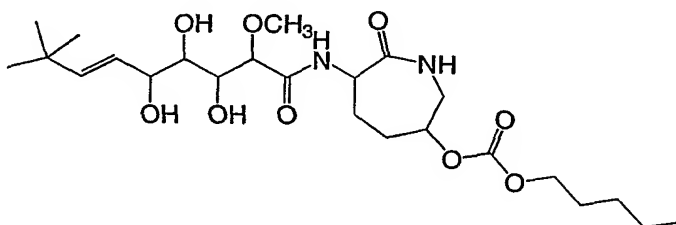
5. A compound according to Claim 4 which is 3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[hexahydro-2-oxo-6-([decyloxy]carbonyl)oxy]-2*H*-azepin-3-yl]non-6-enonamide



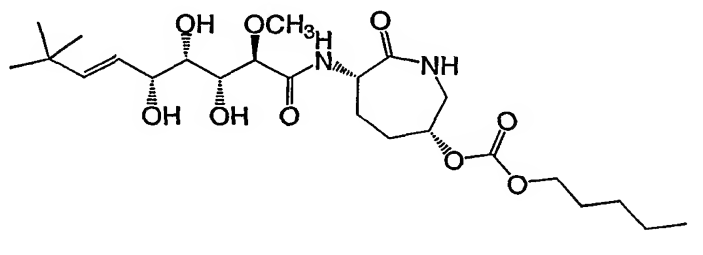
6. A compound according to Claim 4 which is (2*R*, 3*R*, 4*S*, 5*R*, 6*E*)-3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[(3*S*, 6*R*)-hexahydro-2-oxo-6-([decyloxy]carbonyl)oxy]-2*H*-azepin-3-yl]non-6-enonamide having the formula



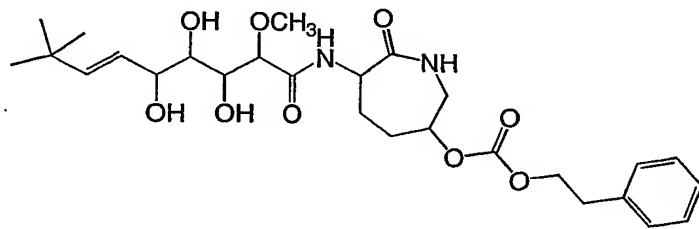
7. A compound according to Claim 4 which is 3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[hexahydro-2-oxo-6-([pentyloxy]carbonyl)oxy]-2*H*-azepin-3-yl]non-6-enonamide having the formula



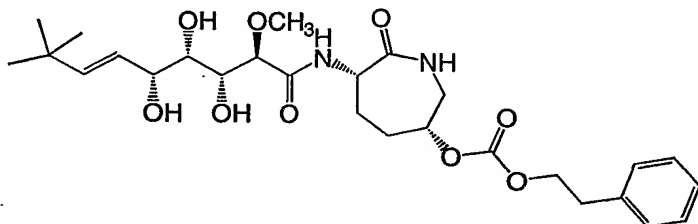
8. A compound according to Claim 4 which is (2*R*, 3*R*, 4*S*, 5*R*, 6*E*)-3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[(3*S*, 6*R*)-hexahydro-2-oxo-6-([pentyloxy]carbonyl)oxy]-2*H*-azepin-3-yl]non-6-enonamide having the formula



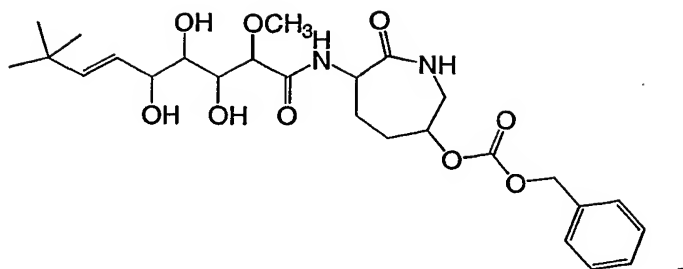
9. A compound according to Claim 4 which is 3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[hexahydro-2-oxo-6-([2-phenylethoxy]carbonyl)oxy]-2*H*-azepin-3-yl]non-6-enonamide having the formula



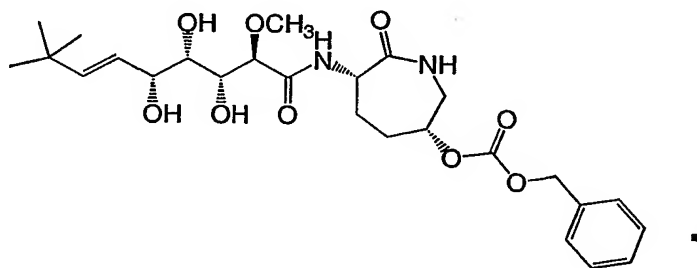
10. A compound according to Claim 4 which is (2*R*, 3*R*, 4*S*, 5*R*, 6*E*)-3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[(3*S*, 6*R*)-hexahydro-2-oxo-6-([2-phenylethoxy]carbonyl)oxy]-2*H*-azepin-3-yl]non-6-enonamide having the formula



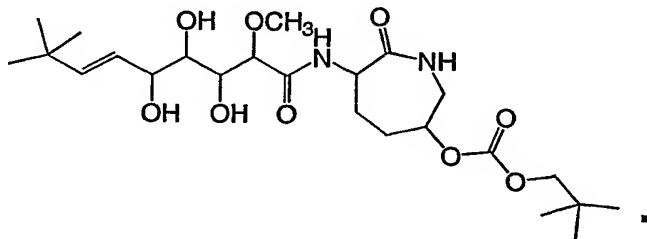
11. A compound according to Claim 4 which is 3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[hexahydro-2-oxo-6-([phenylmethoxy]carbonyl)oxy]-2*H*-azepin-3-yl]non-6-enonamide having the formula



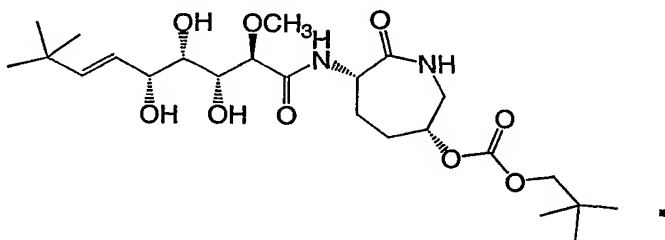
12. A compound according to Claim 4 which is (2*R*, 3*R*, 4*S*, 5*R*, 6*E*)-3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[(3*S*, 6*R*)-hexahydro-2-oxo-6-([phenylmethoxy]carbonyl)oxy]-2*H*-azepin-3-yl]non-6-enonamide having the formula



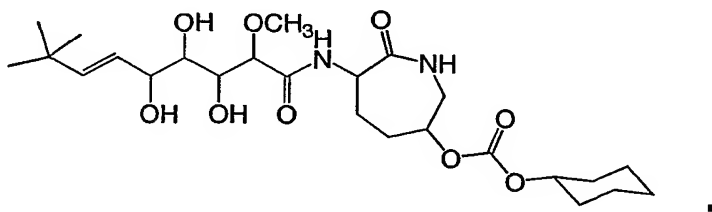
13. A compound according to Claim 4 which is 3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[hexahydro-2-oxo-6-([2,2-dimethylpropoxy]carbonyl)oxy]-2*H*-azepin-3-yl]non-6-enonamide having the formula



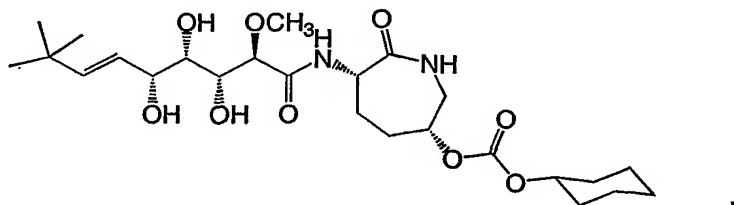
14. A compound according to Claim 4 which is (2*R*, 3*R*, 4*S*, 5*R*, 6*E*)-3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[(3*S*, 6*R*)-hexahydro-2-oxo-6-([2,2-dimethylpropoxy]carbonyl)oxy]-2*H*-azepin-3-yl]non-6-enamide having the formula



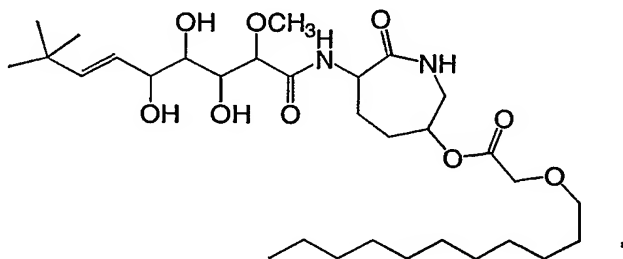
15. A compound according to Claim 4 which is 3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[hexahydro-2-oxo-6-([cyclohexyloxy]carbonyl)oxy]-2*H*-azepin-3-yl]non-6-enamide having the formula



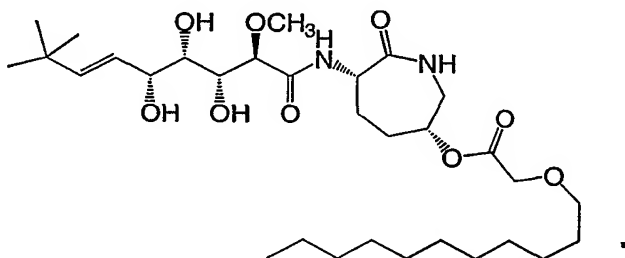
16. A compound according to Claim 4 which is (2*R*, 3*R*, 4*S*, 5*R*, 6*E*)-3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[(3*S*, 6*R*)-hexahydro-2-oxo-6-([cyclohexyloxy]carbonyl)oxy]-2*H*-azepin-3-yl]non-6-enamide having the formula



17. A compound according to Claim 4 which is 3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[hexahydro-2-oxo-6-([undecyloxy]acetyl)oxy]-2*H*-azepin-3-yl]non-6-enamide having the formula



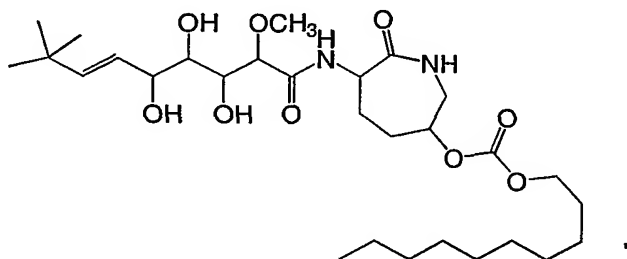
18. A compound according to Claim 4 which is (2*R*, 3*R*, 4*S*, 5*R*, 6*E*)-3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[(3*S*, 6*R*)-hexahydro-2-oxo-6-([undecyloxy]acetyl)oxy]-2*H*-azepin-3-yl]non-6-enamide having the formula



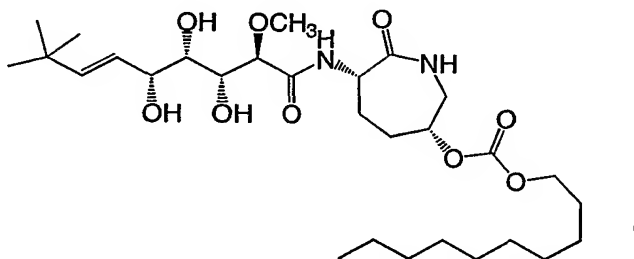
19. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and a therapeutically effective amount of a compound according to Claim 1, or a pharmaceutically acceptable acid addition salt thereof, where possible.
20. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and a therapeutically effective amount of a compound according to Claim 2, or a pharmaceutically acceptable acid addition salt thereof, where possible.
21. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and a therapeutically effective amount of a compound according to Claim 3, or a pharmaceutically acceptable acid addition salt thereof, where possible.

22. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and a therapeutically effective amount of a compound according to Claim 4, or a pharmaceutically acceptable acid addition salt thereof, where possible.

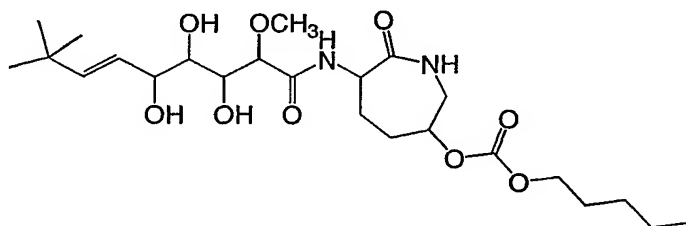
23. A pharmaceutical composition according to Claim 22 comprising a therapeutically effective amount of 3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[hexahydro-2-oxo-6-([decyloxy]carbonyl)oxy]-2*H*-azepin-3-yl]non-6-enonamide having the formula



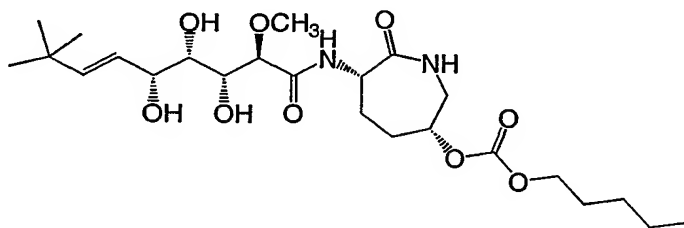
24. A pharmaceutical composition according to Claim 22 comprising a therapeutically effective amount of (2*R*, 3*R*, 4*S*, 5*R*, 6*E*)-3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[(3*S*, 6*R*)-hexahydro-2-oxo-6-([decyloxy]carbonyl)oxy]-2*H*-azepin-3-yl]non-6-enonamide having the formula



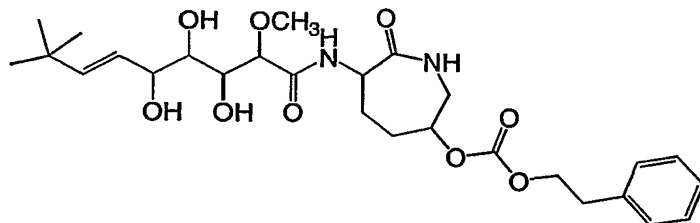
25. A pharmaceutical composition according to Claim 22 comprising a therapeutically effective amount of 3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[hexahydro-2-oxo-6-([[[pentyloxy]carbonyl]oxy)-2*H*-azepin-3-yl]non-6-enonamide having the formula



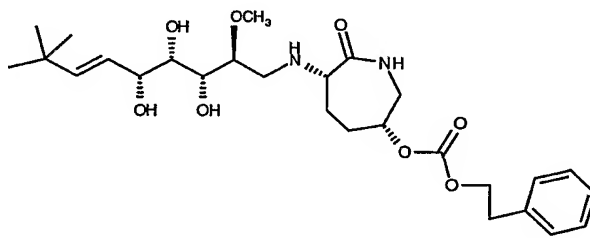
26. A pharmaceutical composition according to Claim 22 comprising a therapeutically effective amount of (2*R*, 3*R*, 4*S*, 5*R*, 6*E*)-3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[(3*S*, 6*R*)-hexahydro-2-oxo-6-([[[pentyloxy]carbonyl]oxy)-2*H*-azepin-3-yl]non-6-enonamide having the formula



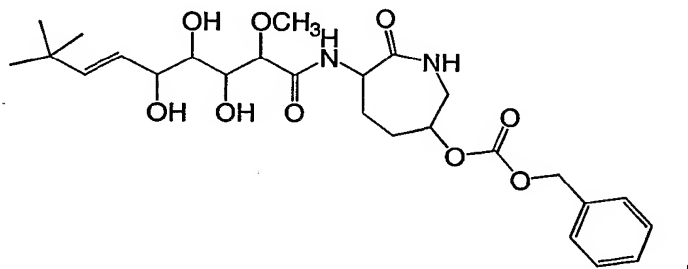
27. A pharmaceutical composition according to Claim 22 comprising a therapeutically effective amount of 3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[hexahydro-2-oxo-6-([[[2-phenylethoxy]carbonyl]oxy)-2*H*-azepin-3-yl]non-6-enonamide having the formula



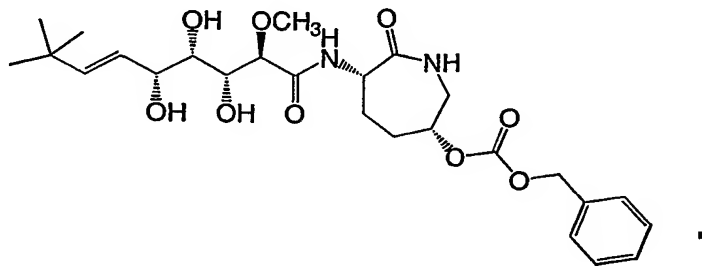
28. A pharmaceutical composition according to Claim 22 comprising a therapeutically effective amount of (2*R*, 3*R*, 4*S*, 5*R*, 6*E*)-3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[(3*S*, 6*R*)-hexahydro-2-oxo-6-([2-phenylethoxy]carbonyl)oxy)-2*H*-azepin-3-yl]non-6-enonamide having the formula



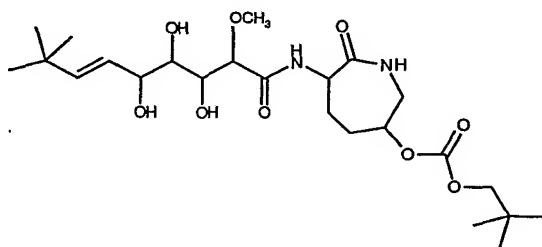
29. A pharmaceutical composition according to Claim 22 comprising a therapeutically effective amount of 3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[hexahydro-2-oxo-6-([phenylmethoxy]carbonyl)oxy)-2*H*-azepin-3-yl]non-6-enonamide having the formula



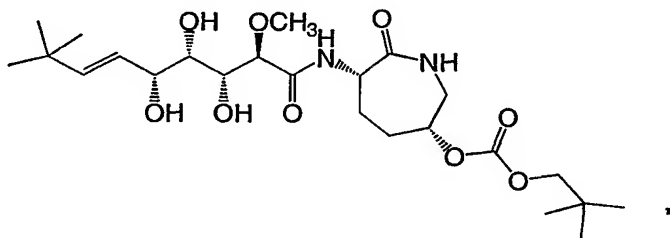
30. A pharmaceutical composition according to Claim 22 comprising a therapeutically effective amount of (2*R*, 3*R*, 4*S*, 5*R*, 6*E*)-3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[(3*S*, 6*R*)-hexahydro-2-oxo-6-([phenylmethoxy]carbonyl)oxy)-2*H*-azepin-3-yl]non-6-enonamide having the formula



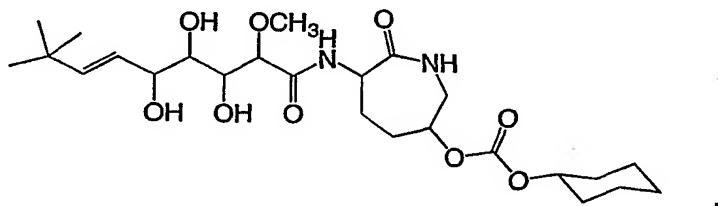
31. A pharmaceutical composition according to Claim 22 comprising a therapeutically effective amount of 3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[hexahydro-2-oxo-6-([2,2-dimethylpropoxy]carbonyl)oxy]-2*H*-azepin-3-yl]non-6-enamide having the formula



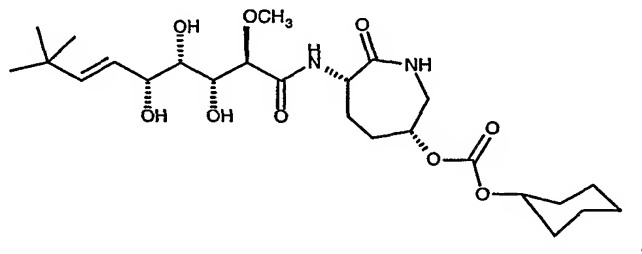
32. A pharmaceutical composition according to Claim 22 comprising a therapeutically effective amount of (2*R*, 3*R*, 4*S*, 5*R*, 6*E*)-3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[(3*S*, 6*R*)-hexahydro-2-oxo-6-([2,2-dimethylpropoxy]carbonyl)oxy]-2*H*-azepin-3-yl]non-6-enamide having the formula



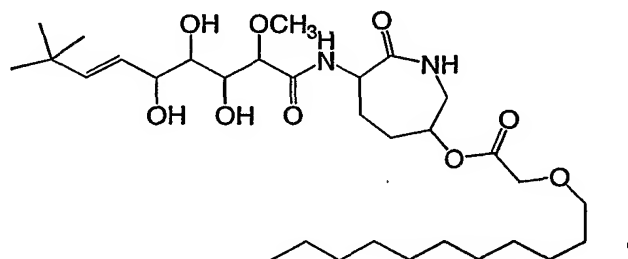
33. A pharmaceutical composition according to Claim 22 comprising a therapeutically effective amount of is 3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[hexahydro-2-oxo-6-([cyclohexyloxy]carbonyl)oxy]-2*H*-azepin-3-yl]non-6-enamide having the formula



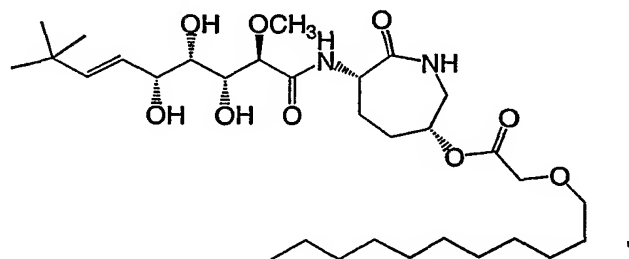
34. A pharmaceutical composition according to Claim 22 comprising a therapeutically effective amount of is (2*R*, 3*R*, 4*S*, 5*R*, 6*E*)-3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[(3*S*, 6*R*)-hexahydro-2-oxo-6-([[cyclohexyloxy]carbonyl]oxy)-2*H*-azepin-3-yl]non-6-enamide having the formula



35. A pharmaceutical composition according to Claim 22 comprising a therapeutically effective amount of is 3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[hexahydro-2-oxo-6-([[undecyloxy]acetyl]oxy)-2*H*-azepin-3-yl]non-6-enamide having the formula



36. A pharmaceutical composition according to Claim 22 comprising a therapeutically effective amount of is (2*R*, 3*R*, 4*S*, 5*R*, 6*E*)-3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[(3*S*, 6*R*)-hexahydro-2-oxo-6-([[undecyloxy]acetyl]oxy)-2*H*-azepin-3-yl]non-6-enamide having the formula



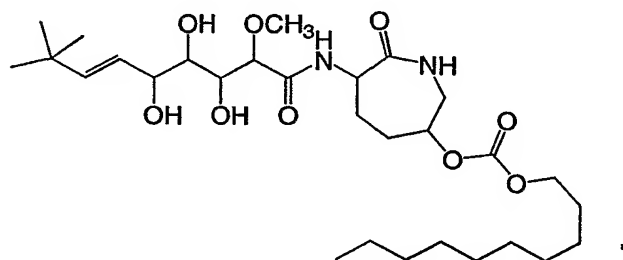
37. A method of treating tumors comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound according to Claim 1, or a pharmaceutically acceptable acid addition salt thereof, where possible.

38. A method of treating tumors comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound according to Claim 2, or a pharmaceutically acceptable acid addition salt thereof, where possible.

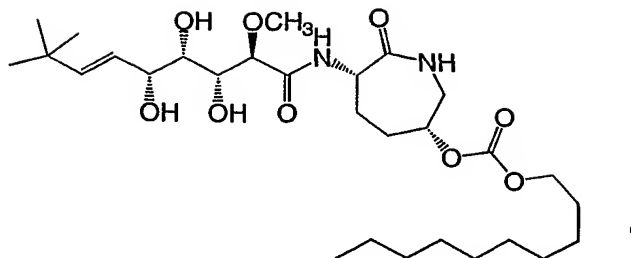
39. A method of treating tumors comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound according to Claim 3, or a pharmaceutically acceptable acid addition salt thereof, where possible.

40. A method of treating tumors comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound according to Claim 4, or a pharmaceutically acceptable acid addition salt thereof, where possible.

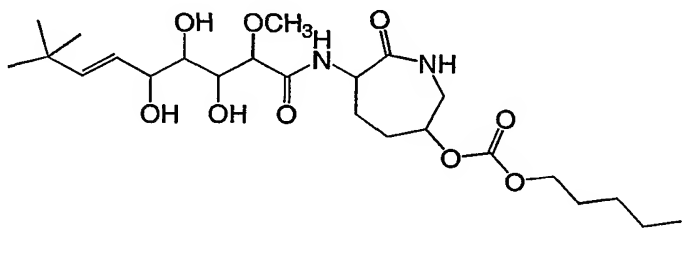
41. A method according to Claim 40 comprising administering to a mammal in need of such treatment a therapeutically effective amount of 3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[hexahydro-2-oxo-6-([decyloxy]carbonyl)oxy]-2*H*-azepin-3-yl]non-6-enonamide having the formula



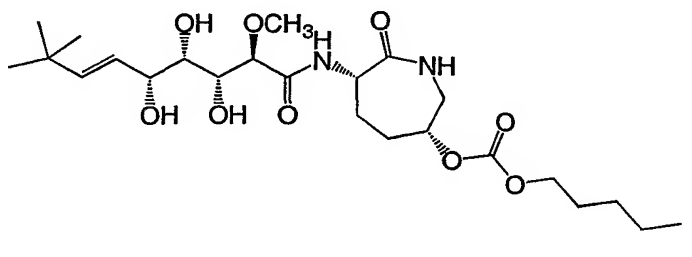
42. A method according to Claim 40 comprising administering to a mammal in need of such treatment a therapeutically effective amount of (2*R*, 3*R*, 4*S*, 5*R*, 6*E*)-3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[(3*S*, 6*R*)-hexahydro-2-oxo-6-([decyloxy]carbonyl)oxy]-2*H*-azepin-3-yl]non-6-enonamide having the formula



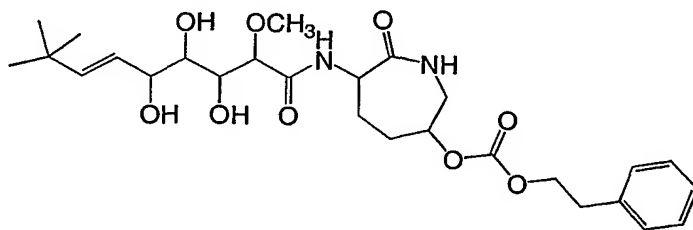
43. A method according to Claim 40 comprising administering to a mammal in need of such treatment a therapeutically effective amount of 3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[hexahydro-2-oxo-6-([[[pentyloxy]carbonyl]oxy)-2*H*-azepin-3-yl]non-6-enonamide having the formula



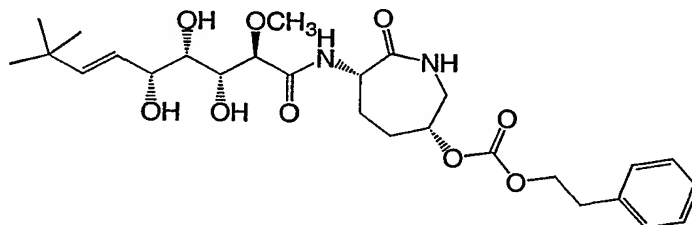
44. A method according to Claim 40 comprising administering to a mammal in need of such treatment a therapeutically effective amount of (2*R*, 3*R*, 4*S*, 5*R*, 6*E*)-3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[(3*S*, 6*R*)-hexahydro-2-oxo-6-([[[pentyloxy]carbonyl]oxy)-2*H*-azepin-3-yl]non-6-enonamide having the formula



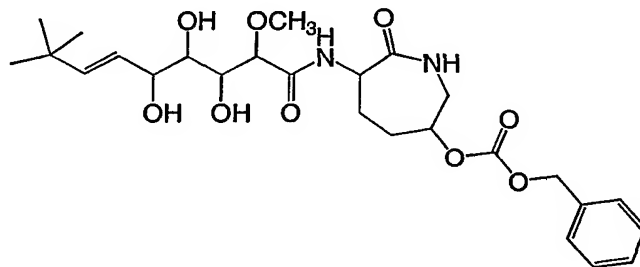
45. A method according to Claim 40 comprising administering to a mammal in need of such treatment a therapeutically effective amount of 3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[hexahydro-2-oxo-6-([2-phenylethoxy]carbonyl)oxy]-2*H*-azepin-3-yl]non-6-enonamide having the formula



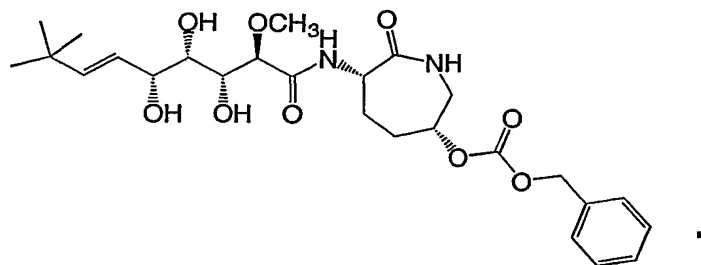
46. A method according to Claim 40 comprising administering to a mammal in need of such treatment a therapeutically effective amount of (2*R*, 3*R*, 4*S*, 5*R*, 6*E*)-3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[(3*S*, 6*R*)-hexahydro-2-oxo-6-([2-phenylethoxy]carbonyl)oxy]-2*H*-azepin-3-yl]non-6-enonamide having the formula



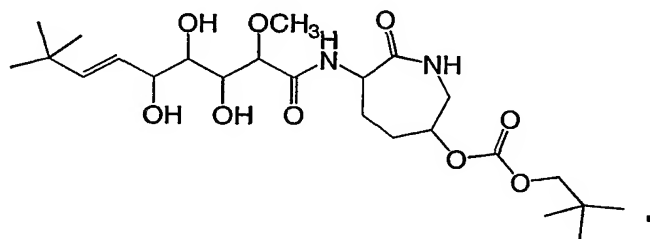
47. A method according to Claim 40 comprising administering to a mammal in need of such treatment a therapeutically effective amount of 3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[hexahydro-2-oxo-6-([phenylmethoxy]carbonyl)oxy]-2*H*-azepin-3-yl]non-6-enonamide having the formula



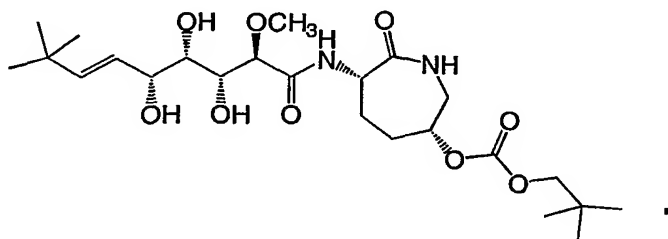
48. A method according to Claim 40 comprising administering to a mammal in need of such treatment a therapeutically effective amount of (2*R*, 3*R*, 4*S*, 5*R*, 6*E*)-3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[(3*S*, 6*R*)-hexahydro-2-oxo-6-([[[phenylmethoxy]carbonyl]oxy)-2*H*-azepin-3-yl]non-6-enonamide having the formula



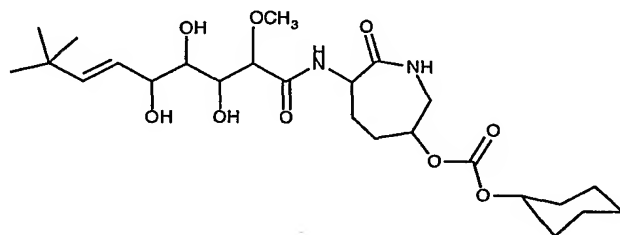
49. A method according to Claim 40 comprising administering to a mammal in need of such treatment a therapeutically effective amount of 3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[hexahydro-2-oxo-6-([2,2-dimethylpropoxy]carbonyl]oxy)-2*H*-azepin-3-yl]non-6-enonamide having the formula



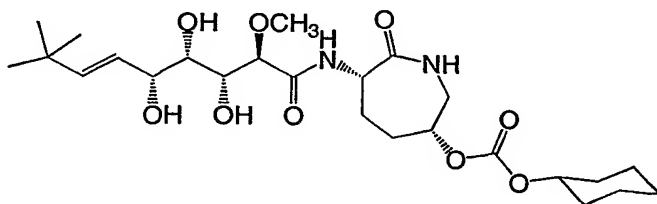
50. A method according to Claim 40 comprising administering to a mammal in need of such treatment a therapeutically effective amount of (2*R*, 3*R*, 4*S*, 5*R*, 6*E*)-3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[(3*S*, 6*R*)-hexahydro-2-oxo-6-([2,2-dimethylpropoxy]carbonyl]oxy)-2*H*-azepin-3-yl]non-6-enonamide having the formula



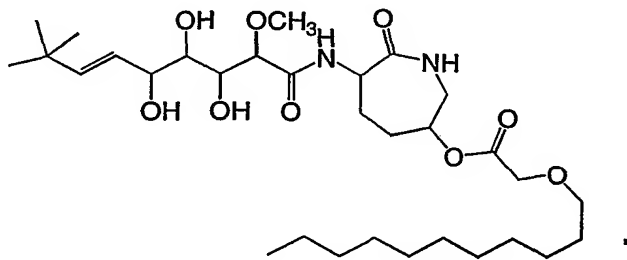
51. A method according to Claim 40 comprising administering to a mammal in need of such treatment a therapeutically effective amount of is 3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[hexahydro-2-oxo-6-([cyclohexyloxy]carbonyl)oxy]-2*H*-azepin-3-yl]non-6-enonamide having the formula



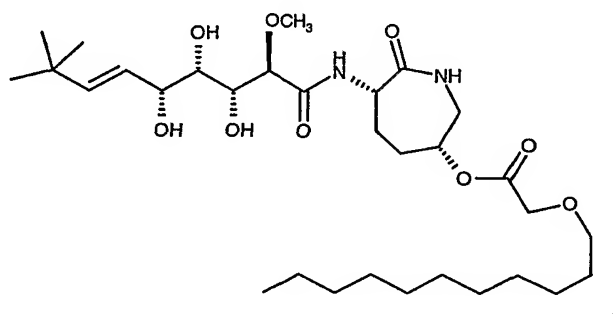
52. A method according to Claim 40 comprising administering to a mammal in need of such treatment a therapeutically effective amount of (2*R*, 3*R*, 4*S*, 5*R*, 6*E*)-3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[(3*S*, 6*R*)-hexahydro-2-oxo-6-([cyclohexyloxy]carbonyl)oxy]-2*H*-azepin-3-yl]non-6-enonamide having the formula



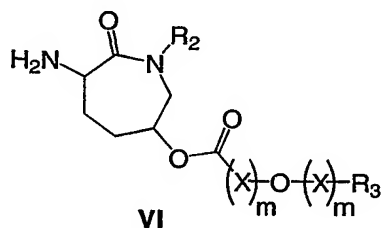
53. A method according to Claim 40 comprising administering to a mammal in need of such treatment a therapeutically effective amount of 3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[hexahydro-2-oxo-6-([undecyloxy]acetyl)oxy]-2*H*-azepin-3-yl]non-6-enonamide having the formula



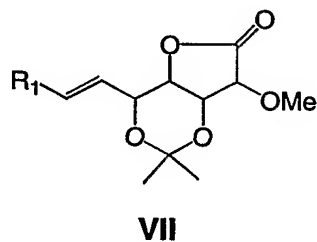
54. A method according to Claim 40 comprising administering to a mammal in need of such treatment a therapeutically effective amount of (2*R*, 3*R*, 4*S*, 5*R*, 6*E*)-3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-*N*-[(3*S*, 6*R*)-hexahydro-2-oxo-6-([undecyloxy]acetyl)oxy)-2*H*-azepin-3-yl]non-6-enonamide having the formula



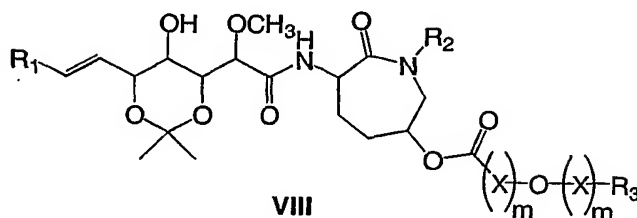
55. A process for preparing a caprolactam compound of formula I according to Claim 1 which comprises, in a first step, acylating an aminocaprolactam compound of formula VI



with a lactone compound of formula VII



in the presence of a polar, organic solvent to obtain a diamide compound of formula VIII



where each of R_1 , R_2 , X , m and R_3 is as defined in Claim 1 and, in a second step, hydrolyzing the diamide compound obtained in the first step by dissolving it in a mixture of solvents to obtain the desired caprolactam compound of formula I.

56. A process according to Claim 55 wherein the acylation step is carried out in the presence of sodium 2-ethylhexanoate, 2-hydroxypyridine, and ethyl acetate at room temperature for 72 hours.

57. A process according to Claim 55 wherein the hydrolysis step is carried out in the presence of a mixture consisting of a protic, organic acid, a protic solvent and an inert, organic solvent.

58. A process according to Claim 57 wherein the hydrolysis step is carried out in the presence of a mixture consisting of trifluoroacetic acid, water and tetrahydrofuran.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 01/05263

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D223/12 A61K31/55 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 831 135 A (CREWS PHILIP ET AL) 16 May 1989 (1989-05-16) cited in the application abstract; claim 1 examples 1-8	1, 37
A	EP 0 687 673 A (PHARMA MAR SA) 20 December 1995 (1995-12-20) compound (IV) page 7, line 50 -page 8, line 25 -/-	1, 37

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

21 September 2001

Date of mailing of the international search report

10/10/2001

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Seitner, I

INTERNATIONAL SEARCH REPORT

Intel onal Application No
PCT/EP 01/05263

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	QUINOA ET AL: "Bengamides, heterocyclic anthelmintics from a Jaspidae marine sponge" JOURNAL OF ORGANIC CHEMISTRY, AMERICAN CHEMICAL SOCIETY. EASTON, US, vol. 51, no. 23, 1986, pages 4494-4497, XP002129550 ISSN: 0022-3263 cited in the application the whole document	1,37
A	ADAMCZESKI M ET AL: "Novel Sponge-Derived Amino Acids. 5. Structures, Stereochemistry, and Synthesis of Several New Heterocycles" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, US, vol. 111, no. 2, 1989, pages 647-654, XP002171012 ISSN: 0002-7863 cited in the application the whole document	1,37

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 01/05263

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			EP 0687673 A1	20-12-1995
			JP 8176124 A	09-07-1996
			US 5891471 A	06-04-1999